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Original Communications

STUDIES ON THE RELATION OF THE CLINICAL MANIFESTATIONS OF ANGINA PECTORIS, CORONARY THROMBOSIS, AND MYOCARDIAL INFARCTION TO THE PATHOLOGIC FINDINGS

WITH PARTICULAR REFERENCE TO THE SIGNIFICANCE OF THE COLLATERAL CIRCULATION

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I. Introduction

This investigation was undertaken in order to gain further insight into the clinical problems associated with angina pectoris, coronary thrombosis, myocardial infarction, and congestive failure by studying the relationship between the clinical manifestations of these conditions and the pathologic changes in the coronary arteries and heart muscle. In a series of 125 consecutive autopsy cases, all subjects were studied who, during life, had had angina pectoris, coronary thrombosis, or congestive failure, or, on post-mortem examination, showed coronary occlusion or myocardial infarction or fibrosis. Recent advances in knowledge concerning the pathologic physiology of cardiac diseases and the availability of new pathologic techniques suggested the desirability of this study. The importance of the collateral circulation in sustaining life in the presence of multiple areas of narrowings and occlusion within the coronary arteries, the pathologic basis for symptoms, and, finally, the cause of death have attracted our particular attention.

II. Method

The technique used in injecting and dissecting the hearts has been previously described in detail[1] and will be only summarized here. The two coronary arteries were cannulated and injected simultaneously with different colored, radiopaque, warm (45° C.) lead-agar masses under a pressure of 150 mm. of mercury. A red-colored mass was injected into the right coronary artery, and a blue-colored mass into the left coronary artery. The mass was immediately hardened by immersion in iced salt solution, and the unfixed heart was opened by a series of incisions which unrolled the heart so that all of the coronary arteries lay in one plane. A roentgenogram of this preparation was made. At no place in the roentgenogram of the unrolled heart was there a shadow of more than a single thickness of the cardiac wall. A complete dissection of the injected, unfixed arteries was then carried out in order to confirm, correct, or extend the observations recorded roentgenologically.

Instead of presenting colored copies of the actual roentgenograms, as in the previous communication,[1] we have prepared a diagram for each heart to illustrate the condition of the coronary arterial tree. These diagrams were prepared as depicted in Figures A, B, and C.

In Figure A is shown a copy of a roentgenogram obtained after the injected heart was unrolled and before the coronary arteries were dissected open.

In Figure B the vessels are tinted, and occlusions and narrowings are noted according to the observations made on opening the vessels under the guidance of the roentgenogram.

Figure C was made by tracing from Figure A the outline of the major arteries and their branches. The areas of narrowing and occlusion, as indicated in this diagram, were disclosed by means of the injection, the roentgenographic film, and, particularly, by the dissection. The arteries found on dissection to be filled with blue mass, which had been injected into the left coronary artery, are denoted by crosshatching. The arteries filled with red mass, which had been injected into the right coronary artery, are denoted by stippling. The vessels filled with mass derived from both arteries, which were therefore purple, are denoted by a combination of stippling and crosshatching. In making these diagrams it was necessary to exaggerate the diameter of the vessels to permit stippling and crosshatching.

As stated previously,[1] three types of anastomotic communications are recognizable. Anastomotic channels may carry blood from one large branch of one of the coronary arteries to another large branch of the same vessel, or may serve to bridge a gap in one of the branches of the vessel. Such anastomoses may be termed left to left (L to L) or right to right (R to R) anastomoses. An obvious R to R or L to L anastomosis is present when there is a definitely occluded zone in one of the coronary arteries, and the distal and proximal parts of the artery are fully injected with mass of the same color.

A second type of anastomosis is found, in which, proximal to a completely occluded point, mass of one color fills a vessel, whereas, distal to the occlusion, mass of another color is present. These are termed left to right (L to R) or right to left (R to L) anastomoses, for the vessels supplying a portion of the myocardium have become entirely dependent upon the opposite coronary artery for their blood supply.

A third form of anastomosis, called convergent anastomosis, is that in which one or more arterial branches receive blood from both coronary arteries. Such vessels, receiving blue mass from the left coronary artery and red mass from the right coronary artery, stain purple.

The contour of the shadow of the injected normal arteries is that of a uniformly tapering band with smooth walls. The course of even the most tortuous vessels is easily followed, and the occasional overlapping of large vessels causes

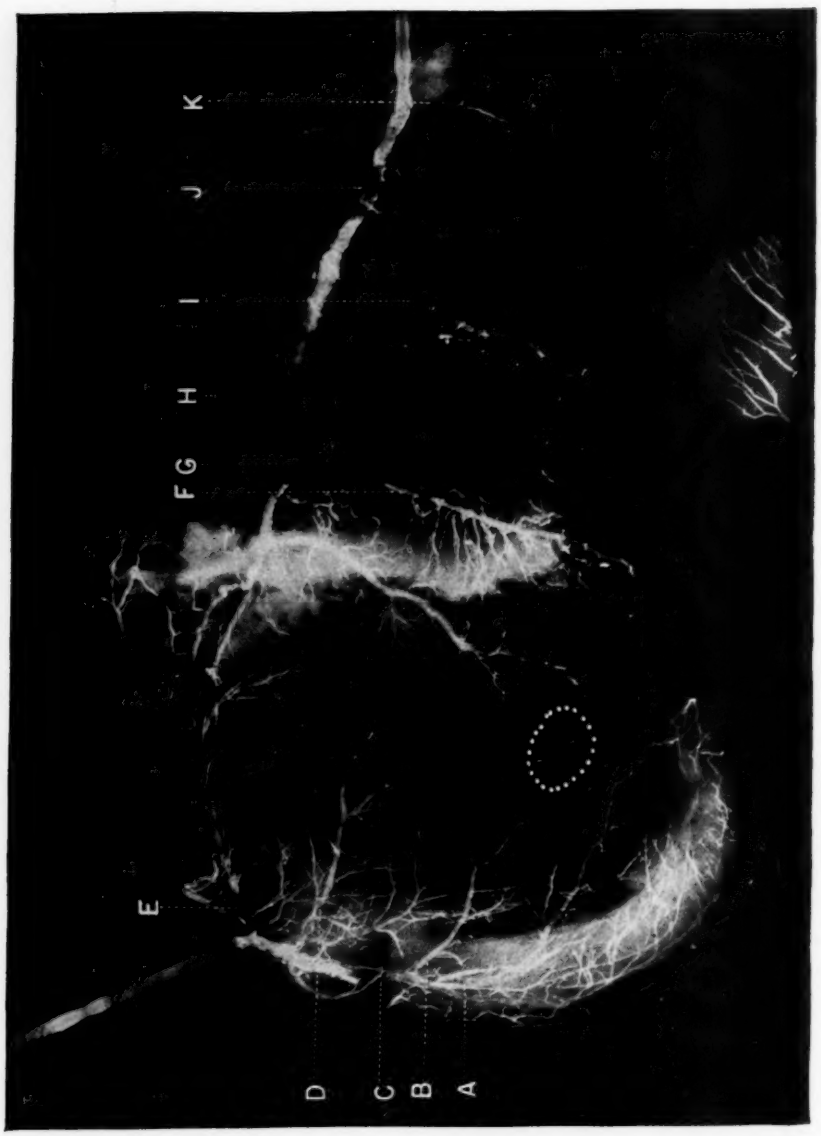


Fig. A.—Copy of roentgenogram of injected and unrolled heart.
A, B, C, D, E, F, I, K = complete occlusions
G, H = emboli
J = fresh thrombus

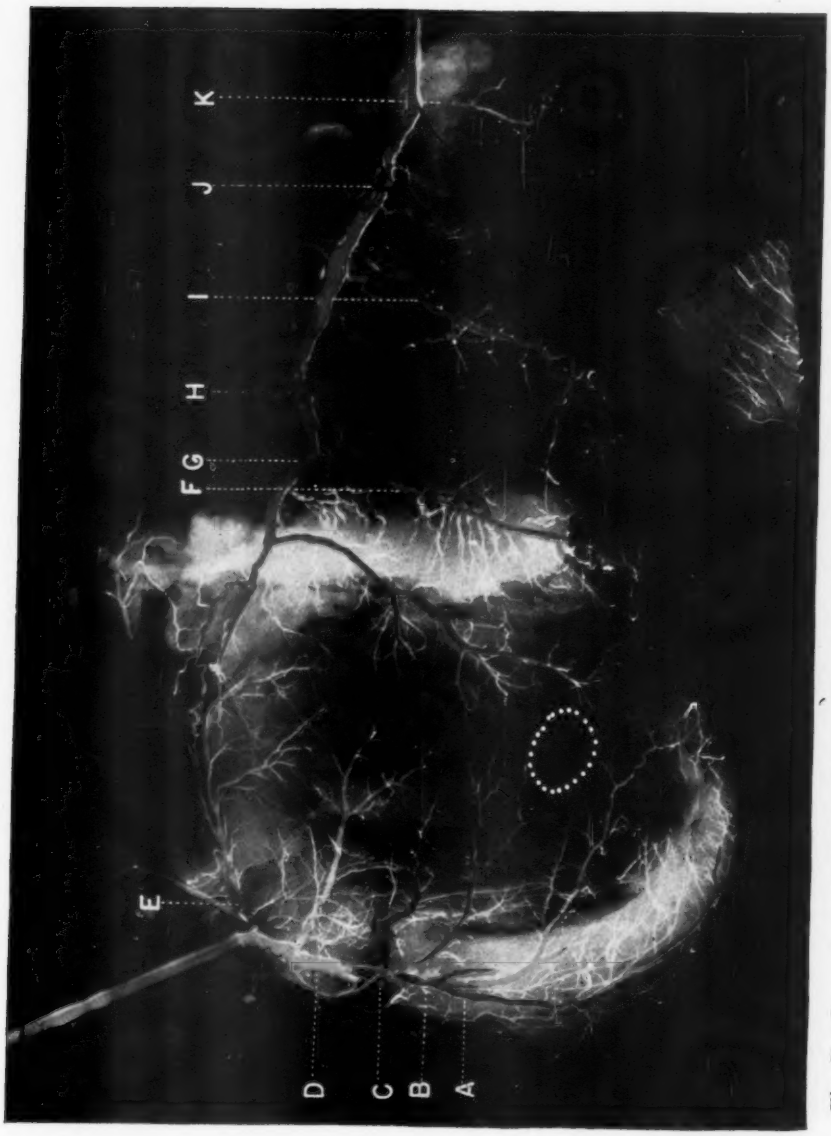


Fig. B.—Copy of roentgenogram of injected and unrolled heart, with arteries tinted to indicate color identified by dissection.

no confusion. The diameters of each vessel and its branches can be easily measured. Because the roentgenographic exposure is made with the pericardial surface in contact with the film holder, the roentgenogram shows almost no distortion of the diameter of the larger, more superficial vessels. The diameter of the smaller, penetrating vessels is, if anything, slightly enlarged, facilitating identification.

Arteriosclerotic plaques which narrow or distort the lumen are easily seen as irregularities in the contour of the shadow of the vessel. Not all such plaques cause a narrowing of the lumen. Some cause a distortion of contour without narrowing. Others may cause no distortion whatsoever and are not detected until the arteries are opened.

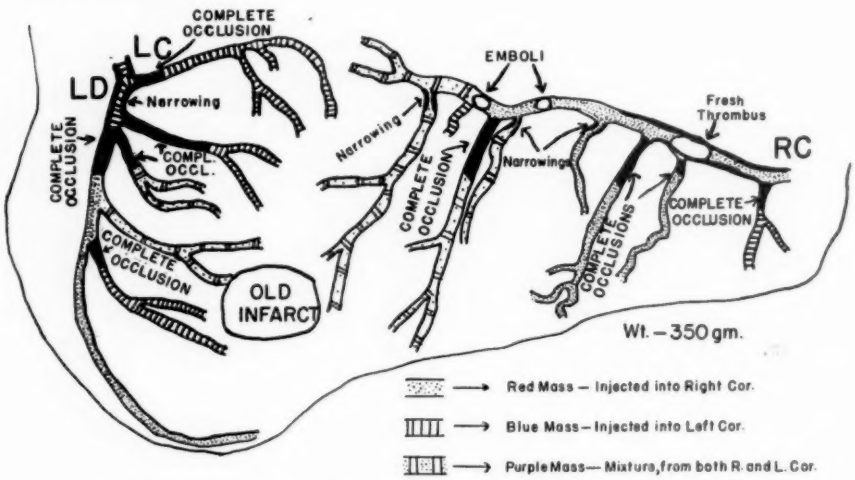


Fig. C.—Diagram made by tracing Fig. A and indicating color as shown in Fig. B, by crosshatching for red, stippling for blue, and a mixture of both for purple. (See Case 4.)

Calcified plaques present a picture interesting in its variations. If the radiopacity of the plaque is the same as that of the injection mass, the shadow of the plaque may fuse with that of the column of injected mass representing the lumen, or may appear as an outpocketing of this lumen. When the lead-agar and the calcified plaque are of different densities, the plaque often stands out quite distinctly.

Zones of complete occlusion usually appear as obvious defects in the shadow of the injected lumen. However, if the occluded zone is calcified, the shadow of this calcium may simulate injection mass in the lumen. No final decision as to the patency or occlusion of any vessel can be made from the roentgenogram alone. This decision is always reserved until after the coronary arteries have been dissected open.

The presence or absence of arterial occlusion is fundamental to the issues discussed in this paper. It should be pointed out, therefore, that no occlusion was considered present unless it could be conclusively demonstrated by dissection and by visualizing the absence of any tinting by injection mass in the occluded portion of the vessel after it was split open.

III. Nature of Material Studied

From a series of 125 consecutive autopsy cases, in which the hearts were injected by the above technique, all cases in which the hearts

showed marked narrowing or occlusion of the coronary arteries, or myocardial infarction or fibrosis, or in which, during life, there had been definite evidences of angina pectoris, congestive failure, or myocardial infarction were selected for further study. Thirty of the 125 cases fulfilled these broad criteria (Tables I, II, III).

Since the purpose of this study was to gain insight into the clinical consequences of pathologic changes, no case was included for detailed discussion unless both an adequate history and physical examination and reliable pathologic data were available. Some patients who were admitted to the hospital on several occasions had histories on each admission, taken independently by House Officers and fourth-year clinical clerks, and had been questioned, in addition, by visiting staff members. Some patients had been followed in private practice by associates in whom we have implicit confidence; others had been seen repeatedly over a period of many years in the cardiac clinic of the hospital. In every case utilized in this study a satisfactory injection was completed, an adequate roentgenogram of the injected heart was obtained, and the dissection was carefully performed and described in detail.

All cases, therefore, in which there had been angina pectoris, congestive failure, or myocardial infarction, were included in this study regardless of the existing cardiac lesions; similarly, every case in which pathologic examination of the heart revealed an occlusion of a major coronary artery or of a primary branch is included, even though no related clinical manifestations were present. In addition, other cases in which the clinical and pathologic data were equally adequate, and in which neither a history of cardiac disease nor a narrowing or occlusion of the coronary arteries nor myocardial infarction or fibrosis was found, were taken from this series of 125 cases for the purpose of establishing the normal anastomotic structure and its relation to age.

Table I lists all of the cases of angina pectoris in which congestive failure was either absent or appeared only after the onset of cardiac pain. No patient with valvular disease is included in this group. We accept the term angina pectoris to denote a syndrome consisting of paroxysmal substernal or precordial pain or discomfort of short duration, not infrequently radiating to the shoulders and inner aspects of the arms, precipitated by exertion, emotion, or other states in which the work of the heart is increased, and relieved by rest or nitroglycerin. Table II lists all of the patients who gave no history of angina pectoris, but were found to have complete occlusion of one or more coronary arteries or major branches thereof. Table III lists those additional cases of angina pectoris in which congestive failure appeared either before, or simultaneous with, angina pectoris, or in which valvular disease was present.

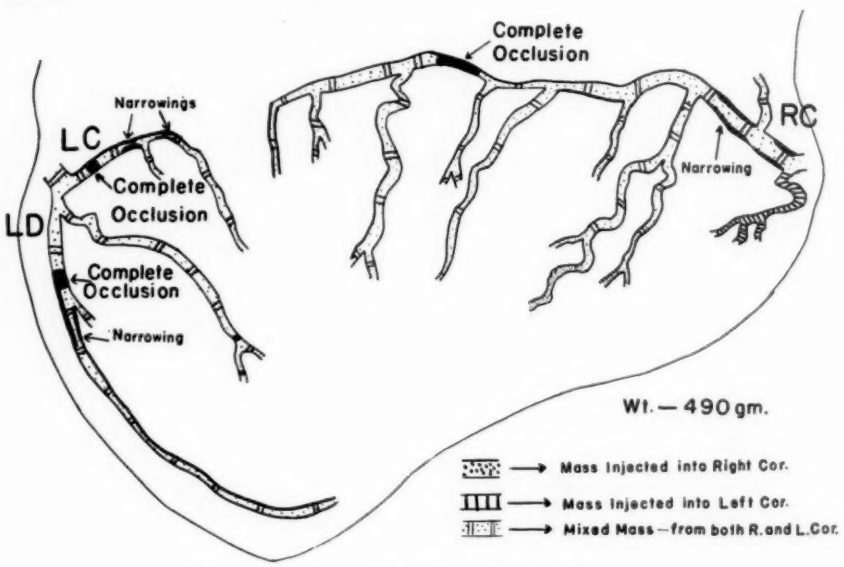
IV. Case Reports With Comments

1. Cases of angina pectoris with or without subsequent congestive failure and without valvular disease - - - - - - (table 1)

a. Cases of old, complete occlusions of all three major coronary arteries

Case 1.—Angina pectoris, ten years; congestive failure, three months; auricular fibrillation; embolism or thrombosis of right femoral artery; gangrene of the right leg, amputation, shock, death.

Mural thrombi in both auricular appendages and the left ventricle; all three major coronary arteries occluded; no recent or old infarcts; rich anastomotic circulation.



Case 1.—Diagram of coronary arterial tree.

History.—A man, W. G., 67 years old, was admitted to the hospital ten days before death, giving a history of angina pectoris of ten years' duration. He was first seen by one of our associates eight years before admission, at which time he was complaining of precordial and substernal pain of two years' duration which was precipitated by exertion and relieved by rest. Throughout the next eight years, during which he was under close medical supervision, the attacks gradually became more frequent and were regularly precipitated by moderate exertion. Over a period of a few months before his final admission to the hospital the attacks became even more frequent and severe, and, in addition, he experienced progressively increasing shortness of breath on exertion, slight orthopnea, and palpitation. Three and one-half months before death a prostatectomy was performed. At this time he had no objective evidence of congestive failure and his cardiac rhythm was normal. A few weeks after this operation, intermittent, sharp pain appeared in the right leg, became progressively worse, and was chiefly responsible for his last admission to the hospital. Until approximately one month before death his cardiac rhythm was normal and he was free of evidences of congestive heart failure, after which gradually increasing signs of congestive failure appeared. Physical examination on admission, ten days before death, showed

dyspnea, orthopnea, distended neck veins, numerous fine râles at the bases of both lungs, and cardiac enlargement with an apex impulse 12 cm. to the left of the midsternal line in the sixth intercostal space. The heartbeat was grossly irregular, with a rate of 130 and a moderate pulse deficit. The blood pressure was 110/75. The right leg was cyanotic and cold from just above the lower thigh downward, and pulsations were absent in the femoral, popliteal, dorsalis pedis, and posterior tibial arteries. The electrocardiogram showed auricular fibrillation with a ventricular rate of 160, low amplitude of the QRS complexes, and diphasic and small T waves in Leads I and II. He was immediately digitalized. Gangrene of the right leg became more pronounced, and a line of demarcation was finally established. Low amputation of the right leg was performed under spinal anesthesia on the ninth day following admission. Postoperatively the heart rate rose to 150. The patient remained stuporous except for short intervals. Approximately eight hours after operation, the heartbeat became regular and very rapid. The respirations became irregular and gasping, and the patient expired at 2:40 A.M. the next day. Death was evidently caused by the toxemia of infection and shock, with terminal paroxysmal tachycardia.

Necropsy.—Heart: The heart weighed 490 grams. Both the left and right ventricles were somewhat hypertrophied. There was patchy, irregularly distributed fibrosis of the left ventricle. There was no evidence, grossly or microscopically, of an old or a fresh infarct. However, near the apex of the left ventricle there was a small ante-mortem thrombus buried among the papillary muscles. There was also a large ante-mortem thrombus in each of the auricular appendages. The valves were essentially normal.

Coronary Arteries: There was marked arteriosclerosis, with calcification, throughout the coronary tree, and old occlusions of all three major coronary arteries were present. The left descending coronary artery was completely occluded a short distance from its origin, but at a point distal to its largest branch. The left circumflex coronary artery also was completely occluded near its origin, and two additional areas of marked narrowing were present distally. The left circumflex artery was rather small; the right coronary artery extended, in its distal part, well over to the left ventricle. The right coronary, likewise, was completely occluded just where it passed over to the left ventricle. All of these vessels were patent distal to the areas of occlusion, and there was a rich anastomotic circulation throughout the heart, for all of the vessels were colored purple.

Comment.—This case of angina pectoris of ten years' duration illustrates the remarkable capacity of an anastomotic circulation to compensate for occlusions, even though all three main coronary arteries were occluded. The injection mass, nevertheless, readily filled the vessels distal to the occlusions; the vessels were colored purple rather than red or blue, demonstrating multiple origins of supply. The remarkable effectiveness of this collateral blood flow is evidenced by the absence of any old infarcts and of congestive failure prior to the last few months of life. The fact that the occlusion of the left descending artery was distal to its largest branch and that that of the right coronary was far removed from the origin of that vessel permitted the large branches to act as the sources of anastomotic blood supply. It is difficult to say how much narrowing or how many occlusions were present in this heart over the period of ten years during which the patient had angina. The well-established anastomotic

TABLE I

CASES OF ANGINA PECTORIS WITH OR WITHOUT SUBSEQUENT CONGESTIVE FAILURE AND WITHOUT VALVULAR DISEASE

CASE NUMBER	NECROPSY NUMBER	AGE—SEX	HEART WEIGHT GM.	CORONARY ARTERIOSCLEROSIS	CORONARY OCCLUSIONS			MYOCARDIAL FIBROSIS	INFARCTION		CLINICAL CORONARY THROMBOSIS		ETIOLOGY	VALVULAR DISEASE	ANGINA PECTORIS, DURATION	CONGESTIVE FAILURE, DURATION	B. P. ELEVATED	CAUSE OF DEATH
					L. D.	L. C.	R.		OLD	RECENT	PAST	TERMINAL						
a. Cases of Old, Complete Occlusions of All Three Major Coronary Arteries																		
1	38-60	67 M	490	+++	M	M	M	++	0	0	0	0	Artsel.	0	10 yr.	3 mo.	0	Postoperative shock—infection.
2	38-21	59 M	610	+++	M	M, M	M	+++	0	0	0	0	Artsel.	0	9 yr.	1 mo.	+	?Vent. standstill or fibrillation.
3	37-49	55 M	560	+++	M	M	M	+	0	+	0	+	Artsel.	0	1 yr.	0	?	Fresh infarction without fresh thrombosis.
b. Cases of Old, Complete Occlusions of Two Major Coronary Arteries																		
4	36-96	53 M	350	+++	M, B, B, B	M	B, B, B, B, (M), (M), (M)	++	+	0*	0	+	Artsel.	0	10 yr.	0	0	Coronary thrombosis
5	37-77	63 F	280	+++	M B	0	M	0	0	+	0	+	Artsel.	0	3 yr.	0	+	?Vent. standstill or fibrillation, 4 weeks after myocardial infarct.

TABLE I CONT'D

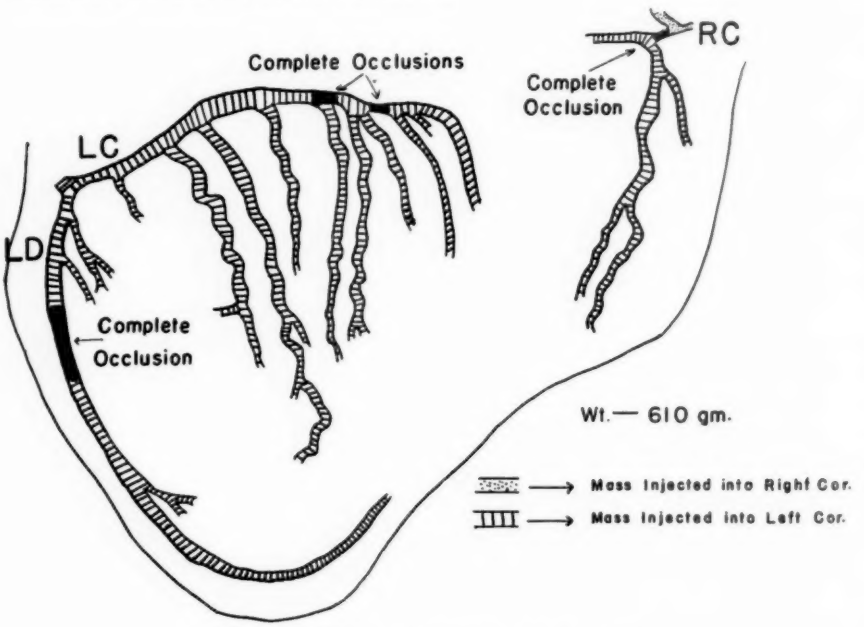
6	38-80	55 M	320	+++	M, B	M	0	+	0	0	+	0	Artscl.	0	4 yr.	3½ yr.	0	Infection and shock, postoperatively.
7	36-84	60 F	510	+++	M	(M)	M	0	0	0*	+	+	Artscl.	0	5 yr.	0	+	Coronary thrombosis.
8	37-63	64 M	510	+++	M	0	M (M)	+	+	0	+	0	Artscl.	0	5 yr.	5 wk.	+	Congestive failure.
9	36-108	67 M	600	+++	0	M	M	+++	+	0	0	0	Artscl.	0	3 yr.	1 yr.	0	Congestive failure.
10	37-11	62 M	500	+++	M	M	0	+++	+	0	0	0	Artscl.	0	9 yr.	1½ yr.	0	?Vent. standstill or fibrillation.
c. Cases of Old, Complete Occlusions of One Major Coronary Artery																		
11	36-110	69 M	380	+++	0	(M)	M	+++	+	0	0	0	Artscl.	0	4½ yr.	10 mo.	+	Carcinoma stomach, hemorrhage, multiple fresh cor. thrombi.
12	37-46	75 M	490	+++	0	0	M, (B)	++	+	0	+	0	Artscl.	0	4 mo.	2 mo.	0	Congestive failure.

M = Old complete occlusion of major coronary artery.
(M) = Fresh occlusion of major coronary artery.
B = Old, complete occlusion of primary branch of major coronary artery.
(B) = Fresh occlusion of primary branch of major coronary artery.
Coronary arteriosclerosis + = slight.
++ = moderate.
+++ = marked.
L. D. = Left descending coronary artery.
L. C. = Left circumflex coronary artery.
R. = Right coronary artery.
* = Fresh infarct might have developed, had sufficient time elapsed ante mortem.

circulation would indicate that most of the occlusions were very old. The presence of thrombi in the auricular appendages and in the left ventricle suggests embolism from this source as the possible cause of obstruction of the femoral artery. Death was evidently caused by postoperative shock and possibly by paroxysmal ventricular tachycardia and fibrillation, since the irregular rhythm of auricular fibrillation was suddenly supplanted terminally by rapid, regular beating.

CASE 2.—Angina pectoris, nine years; arterial hypertension; congestive failure; no symptoms of myocardial infarction; sudden death during sleep while congestive failure was present.

Complete, old occlusions of all three main arteries; no myocardial infarction; rich anastomotic circulation; no fresh occlusions.



Case 2.—Diagram of coronary arterial tree.

History.—A man, E. A., 59 years old, had been studied in the outpatient department at frequent intervals for nine years because of mild attacks of substernal discomfort, and had been closely supervised during his entire illness. Physical examination showed slight cardiac enlargement to percussion; the heartbeat was slow and regular, the lungs were normal. Physical examination was otherwise negative. The electrocardiogram showed inverted T waves in Leads II and III, and marked left axis deviation; a teleoroentgenogram showed that the transverse cardiac diameter was 16.6 cm., and the internal chest diameter, 29.6 cm. In the course of nine years his electrocardiograms showed successive changes in the T waves; the T waves of Leads II and III, at first inverted, gradually became flat or slightly erect. The attacks of angina pectoris increased in severity and frequency; the substernal pain became sharp, and was precipitated by exertion or emotion and relieved by rest and nitroglycerin. Six months before death the patient was admitted to the hospital, where he remained for six weeks, during

which time the attacks continued to recur despite rest in bed. He was readmitted to the hospital two weeks before death because of recurrence of chest pain, increasing shortness of breath, cough productive of bloodstreaked sputum, and occasional attacks of palpitation. At no time had he had a severe attack of prolonged precordial or chest pain. The anginal attacks after admission continued essentially unchanged in severity and other characteristics. Physical examination showed moderate dyspnea, orthopnea, and slight cyanosis. The heart was enlarged to percussion; the beating was slow and regular and gallop rhythm was present. There were moist râles at the bases of both lungs. The liver was enlarged and tender. The blood pressure was 190/120. The congestive failure diminished and the chest pain became less severe and frequent during the twelve days in the hospital. During the night of the twelfth hospital day he died while quietly asleep.

Necropsy.—Heart: The heart weighed 610 grams. There was considerable diffuse fibrous myocarditis throughout, best seen microscopically. There were no old or fresh infarcts, but the myocardium near the apex had a dusky, cyanotic color. This area was not necrotic, but appeared on the verge of necrosis. The valves were normal.

Coronary Arteries: There was much arteriosclerosis throughout the coronary arteries. The right coronary artery was completely occluded just at its origin, and the left descending coronary artery showed a long zone of complete occlusion a short distance from its origin. In the left circumflex coronary artery there were two points of old, complete occlusion near the termination of the vessel. All of the vessels were well injected with blue mass distal to the points of occlusion, and both ventricles were receiving their entire blood supply from the branches of the left coronary artery.

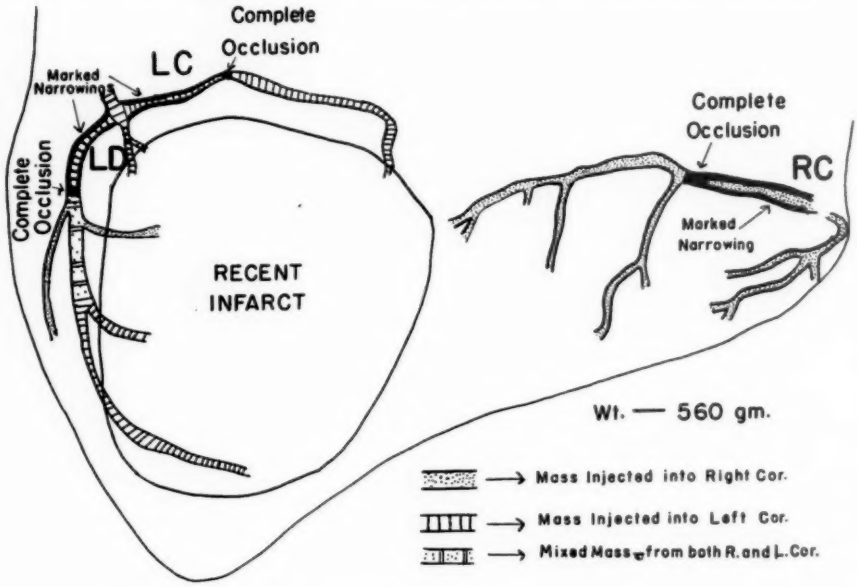
Comment.—This case is of particular interest because all three major coronary arteries had been completely occluded for some time, despite which there were no clinical or pathologic evidences of myocardial infarction. Apparently, during the course of narrowing and occlusion, compensatory circulation had developed uninterruptedly in sufficient degree to prevent infarction. The presence of angina pectoris for nine years indicates, however, that the blood supply had been greatly reduced; the anastomotic circulation, although sufficient to meet the needs of the heart at rest, was nevertheless inadequate on exertion. Myocardial weakness, leading to congestive failure during the last month of life, was caused by the patchy fibrosis and arterial hypertension. The progressive pathologic changes likewise account for the electrocardiographic abnormalities.

The dusky, poorly outlined areas found post mortem near the apex, without any fresh occlusions, were the result of the final, great reduction of blood supply, leading to ischemia even at rest, and possibly to ventricular standstill or fibrillation and consequent death.

In summary, this case portrays the slow progression of arteriosclerotic occlusion of all the main arteries, leading to reduction in the myocardial reserve, angina pectoris, and patchy myocardial fibrosis, and resulting finally in congestive failure without clinical or pathologic evidences of infarction at any time.

CASE 3.—Angina pectoris, one year; no congestive failure; severe, continuous pain, with collapse four days ante mortem, persisting until death.

Old, complete occlusions of all three major coronary arteries; no old infarcts; no fresh occlusions; fresh infarct involving almost the entire left ventricle.



Case 3.—Diagram of coronary arterial tree and site of infarct.

History.—A man, J. S., 55 years old, was admitted to the hospital one day before death, with a history of attacks during the preceding year of severe precordial pain precipitated by exertion and cold, often persisting as long as five minutes, and relieved by rest. Four days before admission he was awakened at night by severe pressure and pain over the anterior chest, radiating to the left arm. He perspired profusely, became ashy pale, and feared that death was impending. During the next three days the pain persisted, but was somewhat less severe. Physical examination on admission showed the syndrome of shock. He was cold, clammy, pale, dyspneic, and cyanotic. The radial pulse was imperceptible and the blood pressure could not be measured. The heart sounds were distant; the beating was regular, the rate, 90. There were numerous râles at the bases of both lungs. The electrocardiogram showed conspicuous bundle branch block. His condition grew worse, and he expired the following day.

Necropsy.—Heart: The heart weighed 560 grams. There was a large, fresh infarct involving almost all of the left ventricle and a portion of the interventricular septum posteriorly. The borders of this fresh infarct were ill defined. In it there was an intermingling of pale muscle, hemorrhagic spots, and more normal-looking muscle. Microscopically, it showed a spotty distribution of acute necrosis with inflammatory exudate. Over it there was a small area of fibrinous, adherent pericarditis. Only a few small endocardial thrombi were found in the ventricle over this area. Besides this large area of fresh necrosis, the myocardium showed only a very slight amount of patchy fibrosis. The injection did not reach a large part of the infarcted area, i.e., it was bloodless, while the remainder was but slightly injected, indicating an obviously inadequate blood supply. Antemortem thrombi were found in both auricular appendages. The valves were normal.

Coronary Arteries: There was much arteriosclerosis, with narrowing, in all three major vessels, especially near their origins. All three major vessels showed points of old, complete occlusion 1.5 to 3.0 cm. from their origins. Dissection revealed no recently deposited thrombi, either proximal or distal to these old occluded points. Vessels were injected beyond the occlusions by anastomotic circulation, but only incompletely, evidently because of the multiple occlusions and widespread narrowing.

Comment.—This heart showed old occlusions, as well as arteriosclerotic narrowing, of all three major coronary arteries. In spite of this the patient had been able to carry on without evidences of congestive failure. Terminally, some slight further impairment of blood flow occurred, possibly because of very slight progression of the atheromatous process in one or more primary branches, or conceivably because of the formation of a fresh thrombus in one of the anastomotic vessels which was not revealed by dissection. The result was immediate, general inadequacy of the entire blood supply of the left ventricle, producing a tremendous infarct. The patient lived for four days after the onset of symptoms and signs of myocardial infarction, suggesting that the area of infarction may not have been as extensive at the onset of the process as at death. This infarct was not entirely the result of a complete lack of blood supply, for part of the infarcted area was slightly injected. The complete occlusions of all three main vessels were old, and antedated the onset of terminal myocardial infarction. Involvement of the posterior portion of the septum was responsible for the electrocardiographic changes.

b. Cases of old, complete occlusions of two major coronary arteries

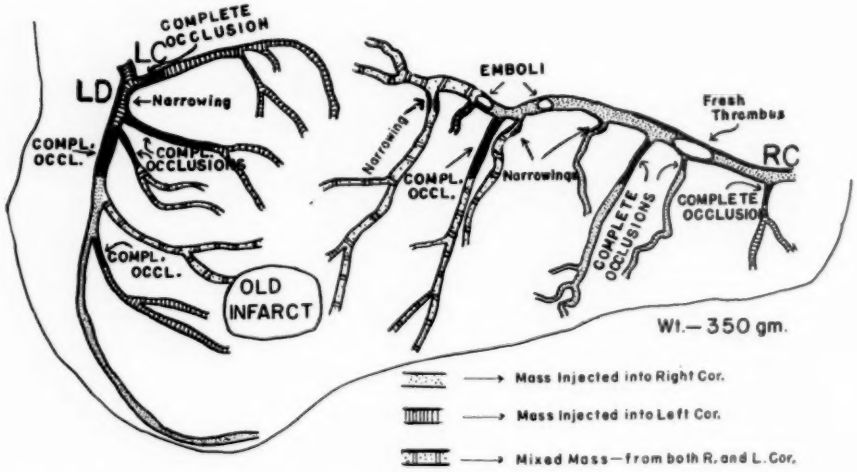
Case 4.—Angina pectoris, ten years; no congestive failure; severe, persistent pain twenty-two hours before death; sudden collapse three hours before death.

Multiple, old occlusions of main left anterior descending and left circumflex arteries; fresh thrombus in right coronary artery with secondary embolism of primary branches distal to thrombus; diffuse myocardial fibrosis and one small area of thinning; questionable old infarct.

History.—A man, M. L., 53 years old, had suffered attacks of precordial and substernal pain during the preceding ten years. He had contracted syphilis 20 years earlier, and had recovered under treatment. The pain was precordial, slight, infrequent, precipitated by exertion, and relieved by rest, until three years before admission, when it became more severe and radiated down the left arm. Rest and nitroglycerin afforded relief. Although the attacks became more frequent and severe, he was able to work continuously until the day of admission. Twenty-two hours before death he experienced persistent, severe, squeezing, substernal pain which was not relieved by nitroglycerin. He nevertheless went to work despite continued precordial pain, but after several hours consulted his physician, who referred him to the hospital at 5 P.M. Physical examination showed little except a gross irregularity of the heart, a pulse deficit, a blood pressure of 118/80, and occasional râles at the bases of the lungs. His distress continued until 2 A.M., when the pain became intense, and the blood pressure could not be measured. He became cold, clammy, and pulseless, and expired at 5 A.M.

Necropsy.—Heart: The heart weighed 350 grams. There were no valvular lesions. The myocardium showed diffuse fibrosis throughout. In the left ventricle,

on the obtuse border of the heart, near the apex, a small area, about 3.0 cm. in diameter, was greatly thinned and almost completely replaced by fibrous tissue. This gave the appearance of a healed infarct. This area was as well vascularized as the remainder of the myocardium. There were no fresh infarcts.



Case 4.—Diagram of coronary arterial tree and site of infarct. (See Figs. A, B, and C.)

Coronary Arteries: All three coronary arteries showed extensive arteriosclerosis, with complete occlusion and obliteration of the lumina over distances as great as 2.0 cm. The main stems of the left anterior descending and left circumflex arteries were completely occluded near their origins. Three main branches of the left anterior descending artery were also completely occluded. Nevertheless, both the left anterior descending and left circumflex arteries distal to the occluded zones were open and well injected, the injection mass reaching them through extensive anastomotic channels. The right coronary artery showed old occlusions of four main branches, and a fresh thrombus occluding the lumen of the main stem 1.5 cm. from its origin. In the same artery, distal to this point, there were two fresh emboli which had arisen from this thrombus. Since these emboli were slightly adherent to the intima, they could not have been dislodged from the parent thrombus by the injection mass. All of the branches representing the distribution of the right coronary artery were well injected distal to both the old and fresh occlusions.

Comment.—This heart affords an amazing example of how complicated, extensive, and unpredictable the compensatory circulation may be. There were nine points of old, complete occlusion, and three points of fresh and complete occlusion. In spite of old, complete occlusions of the main stems of the left circumflex and left anterior descending arteries, complete occlusions of three primary branches of the left descending and four primary branches of the right coronary artery, a new and very complicated anastomotic circulation sufficient to sustain life had developed. Angina pectoris had been present for ten years. Gradual narrowing of the coronary vessels probably gave rise to this extensive anastomotic circulation, which was derived from the right coronary artery and from the portions of the other two main

arteries proximal to the occluded areas. The increasing frequency and severity of the attacks during the final two weeks of life and the development of severe, persistent pain twenty-two hours before death were evidently caused by marked narrowing and, finally, sudden, thrombotic occlusion of the right coronary artery. The absence of pathologic evidence of recent infarction, despite the fact that this occlusion had presumably existed for twenty-two hours, suggests that the patient might have survived even this episode, if secondary embolism from the parent thrombus had not occurred and led to collapse three hours before death. This case also exemplifies the fact that anastomotic circulation, while sufficient to meet ordinary needs, does not provide a wide margin of safety, so that exertion and emotion precipitate angina pectoris and myocardial ischemia. This sequence may lead to focal necrosis and replacement fibrosis.

It is of interest that only one small area of thinning existed, in a portion of the myocardium most remote from the larger vessels. This area, which consisted almost entirely of fibrous tissue, contained some muscle fibers and injected blood vessels, and may represent simple coalescence of small areas of fibrosis in a particularly poorly nourished portion of the heart.

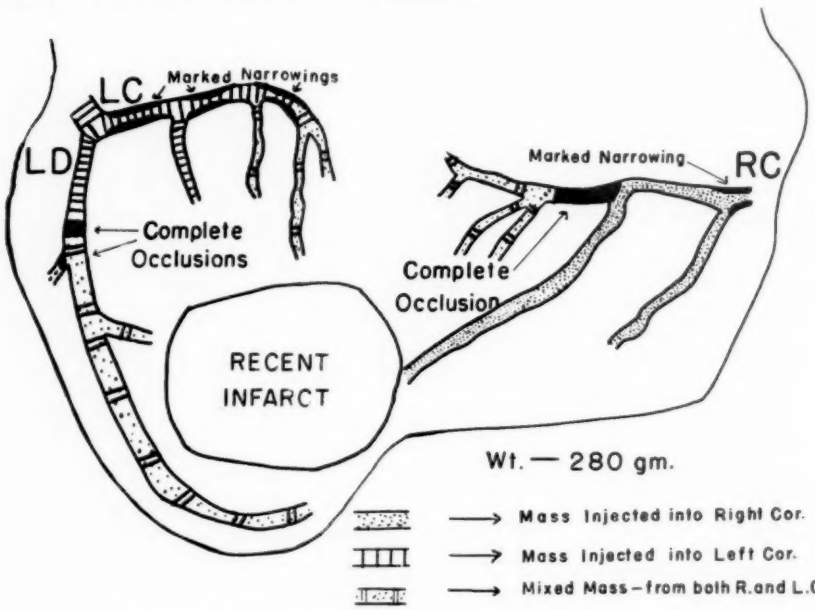
The terminal syndrome of coronary thrombosis, twenty-two hours before death, was caused by the sudden thrombosis of the one remaining patent main artery, the right coronary; collapse three hours before death presumably was the result of the secondary embolism found post mortem. Such embolism is supposed to be rare, but probably is more common than is usually believed (see Case 22, below).

CASE 5.—Angina pectoris, three years; arterial hypertension; no congestive failure; acute myocardial infarction one month before death.

Complete occlusions of main stems of left anterior descending and right coronary arteries; infarction of apex of left ventricle; no fresh thrombus.

History.—A woman, M. C., 63 years old, was admitted to the hospital one month before death. During the previous three years she had had occasional attacks of pain in the left side of the chest anteriorly, radiating to either shoulder, more often to the left arm, precipitated by exertion and relieved by rest and nitroglycerin. The attacks remained approximately unchanged in frequency and severity until six weeks before death, when they became more severe and more frequent, lasting 10 to 15 minutes and occurring several times a day. On the night before admission the attacks recurred at frequent intervals. Each attack awakened her from sleep and none was relieved by nitroglycerin. On the day of admission, four weeks before death, the pain was continuous. During the preceding two weeks the patient had noted some dyspnea on exertion. Physical examination showed no respiratory distress; the heartbeat was slow and regular, the blood pressure 200/110. The lungs were normal. A few hours after admission she suddenly collapsed. Her blood pressure fell to 110/60. Her condition then improved somewhat, although her blood pressure remained low. She was occasionally irrational. The temperature gradually rose to 102° F. Successive electrocardiograms showed that the T wave in Lead I became flat, then inverted. T_2 remained flat and Q_4 was absent. One month after admission she suddenly became very restless, irrational, and pulseless, and expired.

Necropsy.—Heart: The heart weighed 280 grams. There was a large infarcted area occupying the apical portion of the left ventricle. On the endocardial surface of this infarct there was a mural thrombus which was in the process of organization. Sections of the infarcted area indicated that it had been present for weeks; it was undergoing organization and fibrosis. Grossly, there was no fibrosis elsewhere in the heart. The valves were normal.



Case 5.—Diagram of coronary arterial tree and site of infarct.

Coronary Arteries: The coronary arteries showed marked arteriosclerosis, with calcification. The right coronary artery was completely occluded for a distance of about 2.0 cm., starting at a point 8.0 cm. from its origin. The left descending coronary artery was also occluded near its origin for a distance of about 2.0 mm. This occlusion appeared older than that of the right coronary artery. A branch of the left descending coronary artery going to the right ventricle showed a similar, narrow zone of old, complete occlusion. The left circumflex coronary artery showed considerable arteriosclerosis, but no complete occlusion. All of the vessels were well injected beyond the occlusions; purple mass was found throughout the heart, indicating a rich anastomotic circulation. No fresh thrombi were found in any of the vessels.

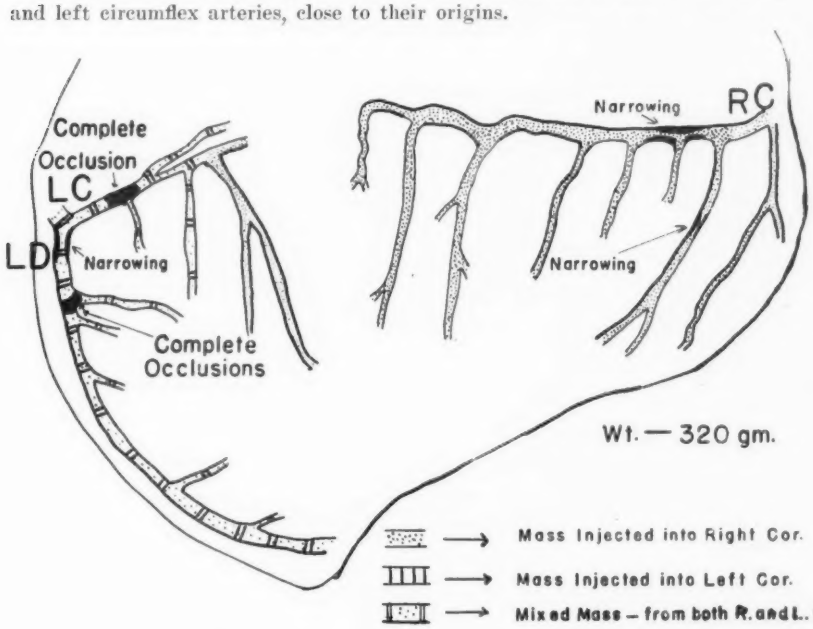
Comment.—The onset of severe pain six weeks before death and the attack of prolonged pain four weeks before death presumably were related to the occurrence of the large infarct in the apical portion of the left ventricle. This healing infarct was probably caused by the occlusion of the right coronary artery, which, on pathologic examination, appeared more recent than the occlusion of the left descending. This case, like Case 8 (see below), is one of infarction of the left ventricle consequent to occlusion of the right coronary artery. The occlusion of the right coronary artery extended over a distance of 2.0 cm., which, in the absence of calcification, suggests organization

of a thrombus in that vessel, rather than a long-standing, progressive, arteriosclerotic occlusion. These findings and the presence of intermingled muscle and connective tissues in the infarct suggest that although a fairly extensive anastomotic circulation had been established prior to the thrombosis of the right coronary, it was not quite adequate. Partial infarction consequently occurred, with healing and considerable vascularization.

The increased severity and frequency of anginal attacks six weeks before death evidently denoted progressive thrombosis of the right coronary artery, and this illustrates the advisability of immediate, complete rest in bed under such circumstances, before the characteristic clinical manifestations of myocardial infarction appear. Lessened cardiac work under such conditions may well prevent or decrease the extent of myocardial infarction and, by prolonging life, provide a fuller opportunity for the development of a compensatory anastomotic circulation.

CASE 6.—Intermittent claudication, left leg, five years; angina pectoris, four years; attack of "coronary thrombosis" three years before death; slight congestive failure; diabetes mellitus; gangrene, left foot, five months; attack of circulatory collapse, without pain, three hours before death; carbuncle of neck; death caused by infection and postoperative shock.

No old or recent myocardial infarction; old occlusions of left anterior descending and left circumflex arteries, close to their origins.



Case 6.—Diagram of coronary arterial tree.

History.—A man, A. D., 55 years old, was admitted to the hospital two weeks before death, complaining of pain in the toes of five months' duration. He had been followed in the outpatient department, where arteriosclerotic changes were

found in both feet. Five years before entry, dull pain appeared in the calf of the left leg after walking, and disappeared after rest. Four years before death, progressive dyspnea and precordial pain on exertion were noted. The pain usually subsided after resting a few seconds or minutes, but sometimes persisted for one-half hour.

Three and one-half years before death he was admitted to another hospital because of a sudden, severe, crushing sensation in the upper precordial region which had come on while he was riding to work in an automobile. He became dyspneic, coughed and wheezed, and finally developed marked weakness and pallor and feared that death was impending. The pain had persisted for two and one-half hours. Physical examination showed ash-gray cyanosis, rapid breathing, cough, and rattling sounds in the throat which completely masked the heart sounds. The blood pressure was 130/110, the pulse rate 140, and the pulse very weak. He responded to treatment by means of tourniquets, venesection, and morphine. Reexamination later showed crackles in both lungs, heart sounds of poor quality, gallop rhythm in the pulmonic area, and a systolic murmur at the apex. The blood pressure was 80/60. He was found to have diabetes and was given insulin. He improved gradually and was discharged seven weeks later with instructions to take ten units of insulin twice daily, and with the recommendation to rest in bed for another month. After discharge he did not complain of shortness of breath, orthopnea, or palpitation. On occasion, however, he did experience pain under the sternum, coming on after excitement or walking against the wind. Progressive arteriosclerotic changes in the left leg resulted in the gradual development of partial gangrene of the third and fourth toes during the five months preceding his final admission. He entered the Beth Israel Hospital two weeks before death because of a carbuncle on the neck and an axillary abscess. Physical examination on admission showed no evidences of congestive failure. There were a large carbuncle on the back of the neck and a small one in the left axilla. The lungs were normal and the edge of the liver was not felt. The blood pressure was 130/65. The heartbeat was regular, and there was a rough systolic murmur at the fifth left intercostal space. The extremities showed extensive vascular changes, absence of arterial pulsations, and ulcers on the third and fourth left toes. The electrocardiogram showed sinus rhythm, a rate of 80, a diaphasic T_2, and an inverted T_4.

One week before death he developed substernal oppression at night which was not relieved by three doses of 1/100 gr. of nitroglycerin and not accompanied by a fall in blood pressure. After one-half hour, 1/6 gr. of morphine was given, which relieved the discomfort. The next day the leucocyte count was 14,600; it had been normal previously. Three days before death, the carbuncles were incised and drained under cyclopropane anesthesia; for two days following this operation he had four to six attacks of angina daily, which were relieved by 1/100 gr. of nitroglycerin. On the morning of the third postoperative day, two weeks after admission to the hospital, he became pallid, dyspneic, cold, and clammy. He had no pain, and there were no tracheal râles. The blood pressure was not obtainable; he expired three hours later. Death was evidently due to infection and consequent shock.

Necropsy.—Heart: The heart weighed 320 grams. There were no old or fresh infarcts, grossly, nor was there any gross evidence of fibrosis. Microscopically, there was some patchy fibrosis. There were no valvular lesions.

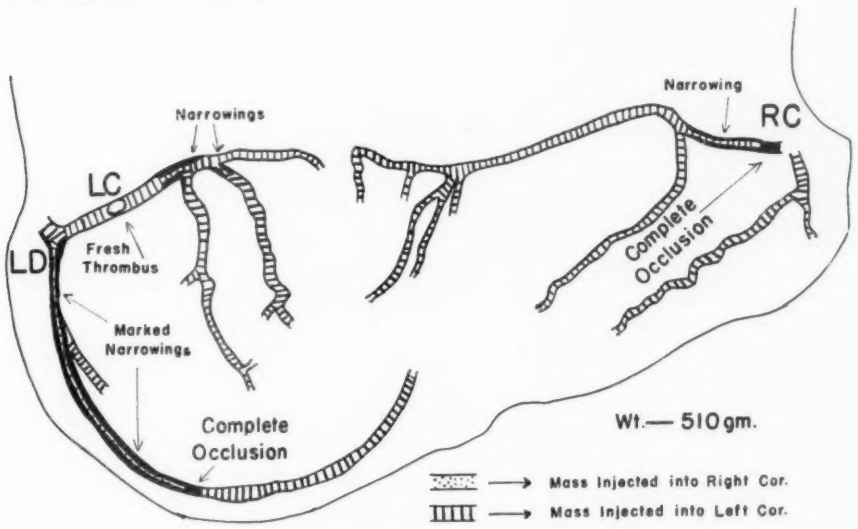
Coronary Arteries: The coronary arteries showed marked arteriosclerosis, with some calcification. There was definite narrowing of the right and left descending coronary arteries near their origins. In the left descending coronary artery there was one point of complete occlusion in the main stem somewhat distal to

this narrowed zone, and another complete occlusion in a main branch just proximal to this area. The left circumflex coronary artery was also completely occluded quite close to its origin. Beyond these three points of occlusion on the left, the arteries were open and fed by an anastomotic circulation coming from the right and left sides of the heart.

Comment.—This is another example of angina pectoris caused by extensive coronary disease. There were old occlusions close to the origins of the two main left arteries and in a large secondary branch. The right coronary artery was narrowed, and, apparently, the anastomotic circulation, although extensive, was insufficient to prevent temporary ischemia under certain circumstances. With the onset of angina, myocardial weakness was also manifested by progressive dyspnea on exertion, but apparently was not progressive after recovery from the attack of severe chest pain, pulmonary edema, and circulatory collapse which occurred three years before death. This attack was characteristic of myocardial infarction, yet the heart showed no evidence of an old infarct or gross evidence of fibrosis. This suggests that the attack occurred after sudden coronary failure caused by a fresh occlusion which produced myocardial ischemia, but that the collateral circulation was sufficient to prevent infarction. Treatment with prolonged rest undoubtedly contributed to recovery to an important extent. The absence of infarction after the final attack, with collapse, may also be explained in this way, but death was probably caused by infection and consequent shock, with coronary insufficiency.

CASE 7.—Angina pectoris, five years; hypertension; no congestive failure; total thyroidectomy three years earlier; "coronary thrombosis"; death.

Old complete occlusions of left anterior descending and right coronary arteries; terminal thrombosis of left circumflex artery; no myocardial fibrosis or infarction; rich collateral circulation.



Case 7.—Diagram of coronary arterial tree.

History.—A woman, R. S., 60 years old, had suffered attacks of squeezing precordial and substernal pain for five years. The pain radiated to the left shoulder, arm, and finger tips, was precipitated by exertion, often persisted for one-half hour, and was associated with dyspnea and palpitation. From the beginning the attacks had been unusually severe, but infrequent, recurring at first approximately once every three to four months. Nitroglycerin afforded only slight relief. She was often incapacitated for four or five days after such attacks. Physical examination revealed a moderately enlarged heart and a blood pressure of 210/120. Laboratory studies showed that she had mild diabetes. The electrocardiogram showed an inverted T wave in Leads I and II. Since the attacks had increased in frequency despite treatment, total thyroidectomy was performed on Oct. 1, 1933. Following this she was completely free from attacks for nineteen months and was able to do her housework. The attacks then recurred. Eight months before death she experienced one attack which was exceptionally severe, although it lasted only twenty minutes. One week later she had two similar attacks, at which time her blood pressure was 112/70. Attacks recurred more frequently, and on Sept. 6, 1936, thirty-five months after thyroidectomy, she was admitted to the hospital complaining of severe substernal pain of thirty hours' duration. She was cold, clammy, cyanotic, and almost pulseless, and the blood pressure could not be obtained. She died one hour after admission.

Necropsy.—Heart: The heart weighed 510 grams. The left ventricle was hypertrophied. The myocardium showed no fibrosis on gross or microscopic examination. There were no valvular lesions and no recent or old infarcts.

Coronary Arteries: The coronary arteries showed marked arteriosclerosis which was confined to relatively limited zones in the larger branches. The greater part of the left anterior descending coronary artery had been converted into an arteriosclerotic cord, with a narrow, tortuous lumen, completely occluded at one point. This occlusion was obviously of long standing. The main stem of the right coronary artery was also completely occluded close to its origin, with marked narrowing of the lumen for a considerable distance distal to the occlusion. The left circumflex coronary artery showed marked, old, arteriosclerotic narrowing of the mouths of two main branches, and complete occlusion of the main stem by a fresh thrombus deposited proximal to the two narrowed branches.

Nevertheless, the coronary vessels were well injected distal to these points of complete obstruction, including the recently deposited thrombotic occlusion. The entire blood supply to the heart had arisen from the left coronary artery, probably largely through the left circumflex branch. The primary and secondary branches of all of the main arteries were relatively patent and capable of utilization for anastomotic circulation. The direction of the blood flow in some of these vessels must have been the reverse of normal. The sudden reduction of flow in the left circumflex artery, caused by a freshly deposited thrombus, must have seriously reduced the total blood supply to the whole heart, although at no place was the myocardium rendered bloodless.

Comment.—This case illustrates the extent to which the coronary arteries can be completely occluded without infarction or even myocardial fibrosis, if the development of collateral circulation keeps pace with the occlusive processes. In spite of long-standing complete occlusion of the main stems of the left anterior descending and right coronary arteries and narrowing of the mouths of two main branches of the left circumflex artery, the rich anastomotic circulation had pro-

vided blood flow sufficient to prevent infarction and even myocardial fibrosis, but not sufficient to prevent anginal attacks. The electrocardiograms showed only inversion of T_1 and T_2. The hypertension was a continuous stimulus to hypertrophy of the heart, and it was becoming more and more difficult to supply enough blood for this constantly increasing bulk of myocardium. The slow progression of the arteriosclerotic process and the performance of total thyroidectomy, by affording time for the development of the rich anastomotic circulation, were probably responsible for the prolongation of the patient's life. The absence of congestive failure is in accord with these pathologic findings. It should be noted that, except for three unusually severe attacks of pain eight months before death, following which the blood pressure was greatly lowered, no attacks suggestive of myocardial infarction had occurred. No infarcts were disclosed post mortem. The unusually severe attacks eight months before death may have been manifestations of occlusions which caused temporary ischemia, but were prevented from producing myocardial infarction by the development of further anastomotic circulation.

Death was unquestionably due to myocardial failure caused by the deposition of a fresh, completely occluding thrombus in the only remaining, patent, main coronary artery, the left circumflex. The absence of post-mortem evidence of myocardial infarction in the area supplied by this artery may have been due to the fact that there was insufficient time for its development before death. The ease with which the vessels distal to the occlusion were injected, however, suggests that infarction might not necessarily have resulted, particularly when one considers that pain and collapse had been present continuously for a period of thirty hours before death.

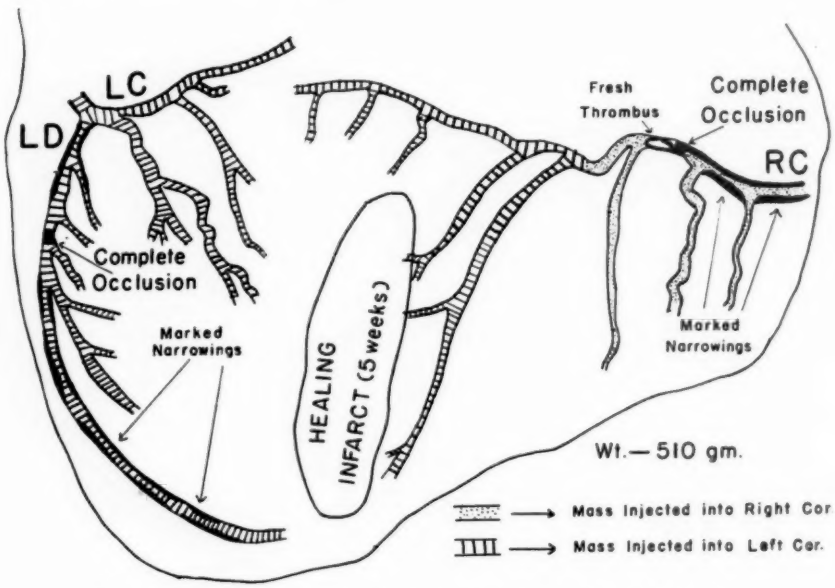
This case clearly exemplifies the absence of any characteristic clinical manifestations of coronary occlusion. The numerous attacks of prolonged anginal pain were presumably due to partial ischemia which developed on exertion or excitement because the collateral circulation, while capable of meeting ordinary requirements, was not sufficient for increased needs. One may postulate that an anginal attack occurred (1) when the myocardial needs became too great, or (2) when narrowing progressed at a rate greater than that of the development of compensatory anastomotic channels.

CASE 8.—Angina pectoris, five years; arterial hypertension; acute myocardial infarction, five weeks old; progressive congestive failure, causing death.

Large, healing infarct with mural thrombus; old, complete occlusions of left anterior descending and right coronary arteries.

History.—A man, M. L., 64 years old, had had attacks of dull pain in the right side of the chest anteriorly, radiating to the left, which were precipitated by exertion and relieved by rest, for five years. Physical examination, on admission to the hospital for a minor surgical condition, three years before death, showed that

the heartbeat was slow and regular. The blood pressure was 170/110. The attacks gradually increased in severity and frequency, occurring three to four times daily and persisting for two to seven minutes. Nitroglycerin was no longer effective, and therefore he re-entered the hospital eight months before death. Physical examination showed that the heartbeat was slow and regular; the blood pressure measured 146/80. A teleoroentgenogram showed slight enlargement of the heart. The electrocardiogram was normal except for a diphasic T_4. Five weeks before death he was admitted to the hospital for the third time, complaining of a very severe attack of sharp, crushing, substernal pain of eighteen hours' duration. The blood pressure on admission was 90/70. The pain radiated to the right and left of the sternum and to both arms. Physical examination showed that the patient was acutely ill and cyanotic, but had no respiratory distress. There was a to-and-fro friction rub over the precordium which persisted for several days. The liver was enlarged, extending three fingerbreadths below the costal margin. There was evidence of fluid in the left pleural sac. The electrocardiogram showed inversion of T_2 and T_3, a deep Q_3, and no Q_4 (old nomenclature). The patient improved somewhat during the first week in the hospital, but signs of congestive failure persisted and gradually increased. During the last week of his hospital stay, general anasarca developed; the patient suddenly had a chill, moderately severe pain over the precordium, took several deep gasps, and expired within a few minutes.



Case 8.—Diagram of coronary arterial tree and site of infarct.

Necropsy.—Lungs: The lungs showed chronic passive congestion, with superimposed acute congestion, edema, and hemorrhage. There were no emboli or patches of pneumonic consolidation.

Heart: The heart weighed 510 grams. A large zone of recent infarction, which was healing, occupied the posterior half of the left ventricle. Over the infarcted area an organizing pericarditis, approximately five weeks old, was observed. As seen by injection, the blood supply to this area was but slightly diminished, as compared with that in the rest of the left ventricle. Microscopically, in this area, patchy fibrosis and slight necrosis were intimately inter-

mingled and irregularly distributed, which is not infrequently seen in a healing infarct. Some of the myocardial changes in portions of this area seemed definitely more than five weeks old, some were of approximately that duration, and some were more recent; none seemed less than a week or ten days old. There was a small thrombus in the left ventricle over the infarcted area. The myocardium elsewhere showed only a few diffuse and tiny fibrotic patches. The valves were entirely normal.

Coronary Arteries: There was an old occlusion of the left descending coronary artery at a point about 4.0 cm. from its origin. Distal to the occlusion, this vessel showed much arteriosclerosis extending well out toward its termination, and leaving only a narrow, insignificant lumen. The left circumflex coronary artery was small and shorter than usual, but otherwise normal. At a point about 5.0 cm. from its origin, the right coronary artery was also completely occluded by what appeared to be an old process. A section of the occluded right coronary artery showed organization within the lumen; some portions appeared to be about five weeks old, and some older. There were also some fresh, tiny, fibrin thrombi in the recanalizing vessels within the organized thrombus. Just beyond this narrow band of older occlusion, between it and the next large branch of the vessel, was a fresh thrombus. Inasmuch as this freshly deposited thrombus was situated in a portion of the right coronary artery which was more or less dead-end, it could not very well have had any sudden influence on the blood supply. It seems to have been a continuation of thrombosis occurring in the canalizing vessels in the neighboring, older, occluded area in this vessel. Almost the whole heart, including the area of recent infarction, was receiving its blood supply from the left coronary branches.

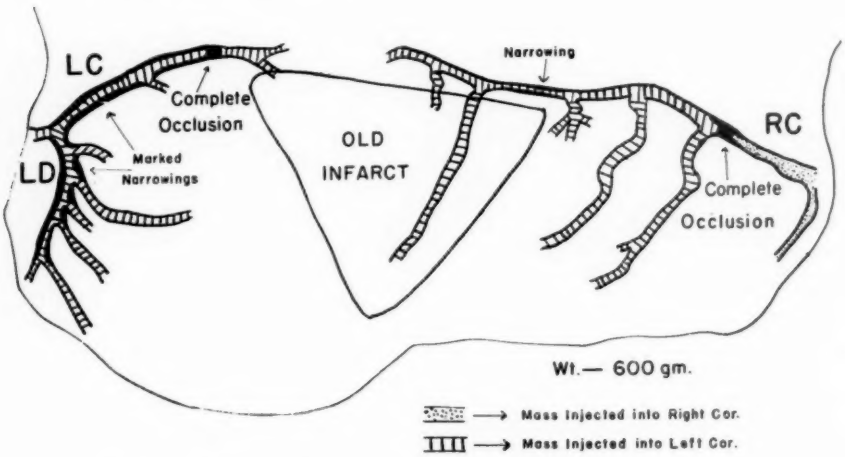
Comment.—This patient was admitted five weeks before death with the clinical manifestations of myocardial infarction, including a pericardial friction rub, which was followed by progressively increasing congestive failure and sudden death.

Post-mortem examination of the heart revealed a large, healing infarct occupying the posterior half of the left ventricle. This infarct appeared to be approximately five weeks old, which would be in accord with the clinical manifestations of coronary occlusion occurring five weeks before death. An occlusion of the right coronary artery, about 5.0 cm. from the origin, appeared to be approximately five weeks old. The occlusion of the left anterior descending artery was calcified, and obviously more than five weeks old; the fresh, occluding thrombus just distal to the older occlusion in the right artery was less than twenty-four hours old. The large area of infarction involving the posterior half of the left ventricle was therefore regarded as resulting from the older of the two occlusions in the right coronary. The infarcted area was patchy in distribution. This case, like Case 5, is one of infarction of the left ventricle caused by occlusion of the right coronary artery. The arterial hypertension and the necessity for anastomotic circulation following prior occlusions of the left descending, and narrowing of the right coronary arteries had reduced the coronary reserve when the infarct occurred. Sudden death in the presence of generalized anasarca may have been caused by a cerebral embolus from the mural thrombus in the left ventricle, or ventricular standstill

or fibrillation following the deposition of the fresh thrombus in the distal portion of the right coronary artery.

CASE 9.—Angina pectoris, three years; congestive failure, one year; fairly rapid progression of both conditions with terminal bronchopneumonia and marked congestive failure.

Complete, old occlusions of left circumflex and right coronary arteries; extreme narrowing and calcification of left anterior descending artery; old myocardial infarction; diffuse myocardial fibrosis.



Case 9.—Diagram of coronary arterial tree and site of infarct.

History.—A man, J.K., 67 years old, had been in diabetic coma ten years previously and had had an infected toe five years previously. For at least three years he had suffered pain and a sensation of pressure over the upper portion of the left side of the chest, anteriorly, which radiated across to the right side of the chest and was precipitated by exertion and relieved by rest and nitroglycerin. Approximately one year before death he noted the onset of dyspnea. Physical examination seven months before death showed moderate obesity, venous engorgement, râles at the bases of both lungs, and slight, but definite, edema of the ankles. The heartbeat was slow and regular, the blood pressure, 130/80. The signs of congestive failure disappeared with rest in bed and the administration of digitalis. He was discharged from the hospital after a stay of one month. Six weeks before death he re-entered the hospital because of progressively increasing congestive failure and frequent attacks of chest pain. Râles were present throughout the lower two-thirds of both lungs, and the liver was enlarged and tender. Two weeks later, after he had improved somewhat, he was allowed to go home, but he re-entered the hospital four days before death because of dyspnea, cyanosis, and fever caused by a superimposed bronchopneumonia. This became more extensive, his cardiac failure progressed, and he expired.

Necropsy.—Heart: The heart weighed 600 grams. There were no valvular lesions. In the posterior part of the left ventricle, over a large area, the muscle was largely replaced by fibrous tissue, but in a patchy manner resembling closely that which is seen in a large, healed infarct. Throughout the myocardium there was much patchy, fibrous myocarditis. There were no fresh infarcts.

Coronary Arteries: Extreme degrees of arteriosclerosis were diffusely manifest in all of the main arteries of the heart. The terminal portion of the main stem of the left circumflex artery was completely occluded. The right coronary was

completely occluded near its origin. The left anterior descending artery showed advanced arteriosclerosis, calcification, and extreme narrowing over a considerable distance, but no complete occlusion.

The right coronary artery proximal to the occlusion supplied only a small part of the myocardium. The greater portion of the right artery was filled with injection mass from the left arteries. Therefore, most of the right ventricle and all of the left ventricle were supplied with blood from the two branches of the left coronary artery. Although anastomotic connections were bridging the several occluded segments, the circulation of the left ventricle was obviously reduced, especially in the fibrosed area.

Comment.—The occurrence of progressive congestive failure is explicable as the result of diminished blood flow and myocardial fibrosis caused by complete occlusion of two main coronary arteries, almost complete occlusion of the third main artery, and marked narrowing of those portions of the arteries which were patent. The attacks of angina pectoris were presumably due to the fact that the blood supply to certain areas of the myocardium was particularly deficient, giving rise to painful stimuli when the heart as a whole was subjected to increased work.

The widespread narrowing and occlusive processes in the coronary arteries of this heart again indicate the extraordinary degree to which anastomotic circulation may compensate anatomically and functionally for defective arterial blood flow.

The large posterior infarct occurred within the distribution of the left circumflex and right coronary arteries. It is more probable that this infarction resulted chiefly from the complete occlusion of the right coronary, which was near the mouth of the vessel, rather than from the occlusion near the distal end of the left coronary artery. The patchy fibrosis of the infarcted area was merely more marked than that found elsewhere. There had been no symptoms indicating that the areas of necrosis resulting in this fibrosis were simultaneously produced. Therefore, the possibility that the infarct in this case represents coalescence of many fibrotic areas in a region which was especially poorly nourished cannot be discarded.

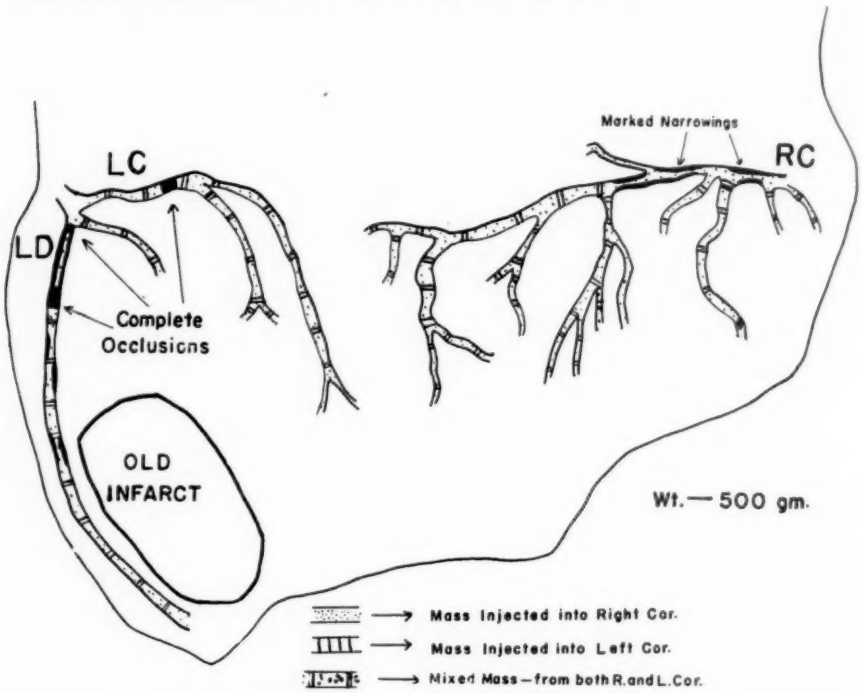
CASE 10.—Angina pectoris, nine years; congestive failure, sixteen months; sudden death, probably caused by ventricular standstill or fibrillation.

Diffuse myocardial fibrosis with one area of old infarction; widespread narrowing and calcification, with old, complete occlusions of left circumflex and left anterior descending arteries; marked narrowing of right coronary artery; no fresh thrombi or infarcts.

History.—A man, L. S., 62 years old, had had attacks of pain under the lower portion of the sternum for nine years, which were precipitated by exertion and relieved by rest. Originally they had occurred two or three times daily, but in the course of two years became less frequent and less severe. He entered the hospital fourteen months before death because of palpitation, breathlessness on exertion, cough, and paroxysmal nocturnal dyspnea during the preceding two months. Physical examination showed cardiac enlargement, gallop rhythm, râles at the bases of both lungs, an enlarged, tender liver, and edema over the legs and

sacrum. The blood pressure was 120/90. The electrocardiogram showed bundle branch block, with a QRS interval of 0.14 sec. Seven days after admission he was discharged improved.

Ten, and again three, weeks before death he was readmitted to the hospital for recurrent congestive failure. The anginal attacks had become less frequent. At the end of the first week of his last stay in the hospital he was free of edema and was permitted to be up and about the wards. He was feeling well and had no signs of failure, when he suddenly expired on the twenty-first day of his stay, while eating breakfast, and without giving evidence of pain.



Case 10.—Diagram of coronary arterial tree and site of infarct.

Necropsy.—Heart: The heart weighed 500 grams. There was much fibrosis, patchy in nature, throughout the left ventricle. There was a large area of almost complete replacement of the muscle by fibrous tissue in the anterior part of the left ventricle. This was interpreted as being a healed infarct. The valves were normal.

Coronary Arteries: There was much sclerosis, with calcification, throughout the coronary arteries. The left descending artery was completely occluded for a distance of 5.0 cm. The left circumflex artery was a small vessel and was also completely occluded a short distance from its origin. There was marked narrowing of the beginning of the right coronary artery, but no complete occlusion. No fresh thrombotic occlusion was present. There was a rich anastomotic arterial circulation among all of the vessels; all of them received blood in varying proportions from both left and right coronary arteries proximal to the occlusions. The infarcted area was less vascular than other portions of the heart.

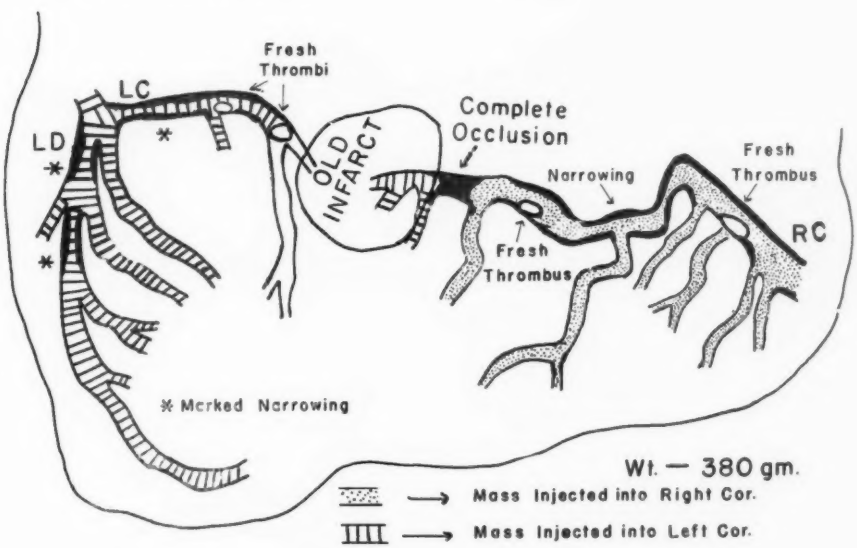
Comment.—The occurrence of congestive failure in this case, as in Case 9, is comprehensible because of the widespread obstruction to coronary flow, causing diffuse patchy fibrosis of the myocardium. De-

spite complete occlusion of the left circumflex and left anterior descending arteries and marked narrowing of the right coronary artery, but one area of complete replacement of muscle by connective tissue was found. Whether this area developed slowly as the result of gradual replacement, or whether it represented an infarct which was suddenly precipitated by acute coronary thrombosis in the past, cannot be stated. As in Cases 4, 9, and 11 (see below), the blood supply to one area of the heart was evidently considerably more reduced than to the rest, and this may have been responsible for the angina pectoris. No terminal or recent thrombosis was found; death was probably caused by ventricular standstill or fibrillation.

c. Cases of old, complete occlusion of one major coronary artery

CASE 11.—Angina pectoris, four and one-half years; slight congestive failure, ten months; hypertension, weakness, anorexia, and terminal hematemesis caused by carcinoma of the stomach.

Generalized arteriosclerotic narrowing of all coronary arteries; old occlusion of right coronary artery; multiple, fresh, ante-mortem thromboses of right coronary and left circumflex arteries; diffuse myocardial fibrosis, particularly marked in two areas; questionable infarction.



Case 11.—Diagram of coronary arterial tree and site of infarct.

History.—A man, J.W., 69 years old, had had precordial and substernal pain, which was precipitated by exertion and relieved by rest, for four and one-half years. Ten months before death he was admitted to the hospital because of dyspnea, palpitation, weakness, epigastric distress, and anorexia. Physical examination showed moderate cyanosis and dyspnea, musical râles throughout the chest, and a few moist râles at the bases of the lungs. The heart was moderately enlarged, the rhythm normal, and the rate 80. The blood pressure was 180/110. The liver was not felt. The electrocardiogram showed intraventricular block;

the QRS was notched and its duration was 0.12 second. During his stay in the hospital he improved but slowly; he had one severe attack of choking pain in the chest, which radiated to his arms, requiring morphine. He was discharged after four weeks, still showing minimal signs of congestive failure. He was reasonably well except for the attacks of precordial and substernal pain which became more severe and more frequent about one month before his last admission. This final admission, a few days before death, was occasioned by a large hematemesis. Physical examination showed a moderate degree of shock. The lungs were normal, the heartbeat rapid and regular. There were resistance and tenderness in the epigastrium. The blood pressure was 80/65. In spite of treatment, the gastric bleeding could not be controlled; his condition became worse, and he died four days later.

Necropsy.—Necropsy showed that carcinoma of the stomach was the source of the hematemesis.

Heart: The heart weighed 380 grams. Microscopically, it showed much diffuse fibrosis, particularly in the posterior part of the left ventricle near the base, and also at the base of the septum, where, in one area, 4.0 cm. in diameter, there was complete replacement of muscle by fibrous tissue. This infarct was well vascularized and was considered to be old. There were no fresh or recent infarcts. The valves were normal.

Coronary Arteries: All three main coronary vessels showed marked arteriosclerosis, with calcification and narrowing throughout. The right coronary artery showed an old, complete occlusion at its distal end, beyond which the vessel contained injection mass from the left coronary vessels. In two places proximal to the old occlusion in the right coronary artery, and in two places in the left circumflex artery there were fresh, stringy, ante-mortem thrombi which obviously had been deposited just before death. The more distal thrombus in the left circumflex artery completely occluded the lumen, and no injection mass was found beyond this thrombus; the other three thrombi only partly occluded the lumina.

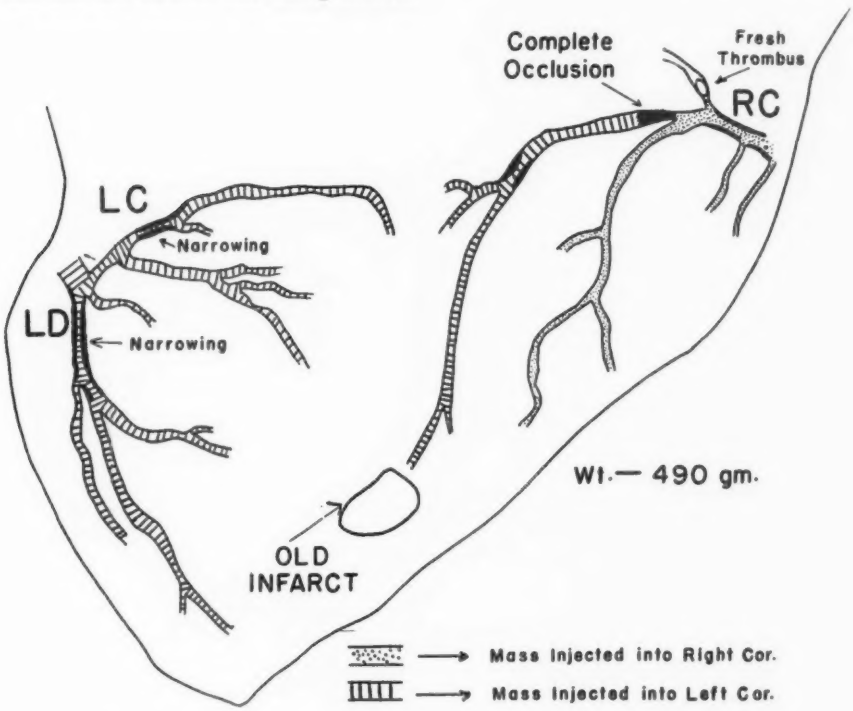
Comment.—This case is particularly interesting because the intervention of a fatal noncardiac disease afforded an opportunity to examine the myocardium and coronary vessels at a stage of angina pectoris compatible with continued life. Prior to the fatal hematemesis, which led to shock and the deposition of fresh thrombi in the coronary arteries, the heart had obviously suffered from impaired circulation. There were generalized arteriosclerotic narrowing and calcification of all of the main coronary vessels, with complete occlusion of the right artery. The narrowing involved particularly the mouths of the arteries. The congestive failure and the diffuse myocardial fibrosis were consequences of the reduced blood flow, as in Cases 9 and 10. The occurrence of angina pectoris may well have been related to the fact that the area of advanced fibrosis was nourished particularly poorly because of the old occlusion in the right coronary artery. This area of fibrosis represented either an old, silent infarct, or the coalescence of many small fibrotic areas. The involvement of the septum by this process accounted satisfactorily for the electrocardiographic changes.

This case also illustrates the danger of shock, from any cause, in cases of advanced arteriosclerotic involvement of the coronary arteries. The sudden deposition of fresh thrombi would probably have caused

cardiac collapse even if the gastric hemorrhage itself had ceased. The absence of injection mass beyond the completely occluding thrombus in the left circumflex artery indicates that pathologic evidence of infarction would have been found, had the patient survived somewhat longer. It is also probable that eventually the other thrombi would have completely occluded the lumina by gradual accretion of platelets and fibrin.

CASE 12.—"Indigestion," six months; attack of prolonged cardiac pain, four months before death; attacks of angina pectoris, four months; congestive failure for two months, gradually increasing and causing death.

Diffuse myocardial fibrosis; old infarct at apex, mural thrombus in right auricle, old, complete occlusion of right coronary, arteriosclerotic narrowing of left circumflex and left anterior descending arteries.



Case 12.—Diagram of coronary arterial tree and site of infarct.

History.—A man, S. G., 75 years old, entered the hospital two weeks before death, complaining of "indigestion," precordial pain, dyspnea, and nocturnal dyspnea. The indigestion had begun six months before and was characterized by anorexia, sour eructation, belching, and some epigastric pain. Four months before death he experienced an attack of severe precordial pain radiating to the left arm, which persisted for several hours and led him to remain voluntarily in bed for two days. After this he developed similar but milder attacks of a few minutes' duration, which were precipitated by exertion and emotion and relieved by rest and nitroglycerin. Two months before admission his physician had found evidence of congestive failure. Thereafter the patient suffered several attacks of nocturnal dyspnea. During the two weeks before admission he had many attacks of angina pectoris and noted increasing dyspnea on exertion.

Physical examination showed a slow, regular heartbeat and râles at the bases of the lungs. The blood pressure was 150/90. The electrocardiogram showed a depressed S-T interval in Lead I, a slightly diphasic and low-voltage T wave in Lead II, and right axis deviation. During his two weeks in the hospital his congestive failure became progressively worse, the dyspnea finally became intense, and he died of congestive failure.

Necropsy.—Lungs: The lungs showed nothing unusual, such as emboli or infarcts.

Heart and Coronary Arteries: The heart weighed 490 grams. There was diffuse fibrosis throughout the myocardium. Near the apex there was a very small area, 1.5 to 2.0 cm. in diameter, which showed thinning and marked fibrosis. Microscopically, this area appeared to be a healing infarct at least a few months old. No active inflammatory reaction was present. All vessels leading to this area were patent, and the area was well injected. In the right auricle a large, crumbly, ante-mortem thrombus was adherent to the endocardium, underlying which considerable degeneration was found. In this area there was a large, freshly thrombosed branch of the right coronary artery. This branch constituted the main blood supply of the auricles and the S-A and A-V nodes. There were no valvular abnormalities.

There was an old, complete occlusion of the right coronary artery, 3.0 cm. from its origin; the portion of this vessel distal to the occlusion was filled from the left coronary artery. The left anterior descending artery was markedly narrowed; a few areas of atheromatous change, with calcified spots, were present throughout the left circumflex artery. There were no fresh thrombi in the vessels supplying the ventricles.

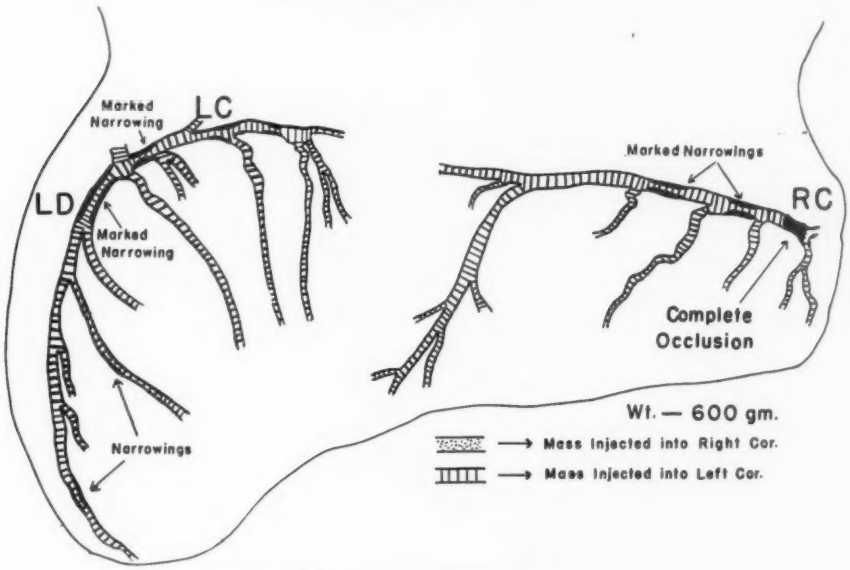
Comment.—Angina was of very short duration in this patient (only four months, which is the shortest in this series). This was the oldest patient (75 years), and the heart was one of the only two of this series (Table I) in which but one main vessel was occluded. Theoretically, the area in the region of the apical infarct could have been supplied through anastomotic circulation by the terminal branches of any of the three major coronary arteries, and probably depended on circulation from the left circumflex and left anterior descending arteries. The severe pain four months before death was evidently caused by the small myocardial infarct near the apex. It is possible that this small infarct was the result of sudden occlusion of the previously narrowed right coronary artery, or that it represented coalescence of patchy areas of fibrosis. The presence of coronary arteriosclerosis in the left circumflex and left anterior descending arteries, combined with complete occlusion of the right coronary, was evidently responsible for the area of fibrosis. This area was farthest removed from the sites of anastomotic circulation. The occurrence of death from congestive failure is to be related to the generalized insufficiency of the coronary circulation, which resulted in diffuse, patchy necrosis of muscle fibers and replacement fibrosis.

2. CASES OF CORONARY ARTERIAL OCCLUSIONS AT NECROPSY IN WHICH THERE HAD BEEN NO ANGINA PECTORIS DURING LIFE – – – – (TABLE II)

a. Cases of complete occlusion of at least one major coronary artery or primary branch, without infarction

CASE 13.—Progressive congestive failure; arterial hypertension; no history of cardiac pain; dyspnea on exertion, and weakness, one to two years; edema of legs, three months; cerebral hemorrhage.

Old, calcified occlusion of right coronary artery near its origin; widespread, advanced coronary arteriosclerosis, with narrowing of all main vessels; calcific aortic stenosis; no infarcts or fibrosis; rich anastomotic circulation.



Case 13.—Diagram of coronary arterial tree.

History.—A man, M. G., 75 years old, was admitted to the hospital four days before death because of cerebral hemorrhage. His history was obtained from members of his family and his physician, a member of the hospital staff who had observed him closely for several years. The patient was known to have had hypertension for three years, and had experienced gradually increasing dyspnea on exertion and weakness for one to two years. Three months before admission the dyspnea became somewhat more marked, and swelling of both legs half way up to the knees was noted. He had then stayed in bed for one week, and was apparently doing well until the afternoon of the day of admission, when he had three convulsions and became unconscious. There was no history of cardiac pain or precordial discomfort at any time before or during the present illness. On admission, physical examination showed drowsiness, confusion, and slurred, rambling speech. The heart was enlarged to the left, and the heartbeat was slow and regular. There was a high-pitched, rough, systolic murmur, loudest at the apex. The blood pressure was 180/100. There was edema of the lower extremities as high as the sacrum, and Kernig's sign was present on both sides. In the course of the next few days he became progressively worse and expired.

Necropsy.—Brain: There were cerebral hemorrhage and edema.

Heart: The heart weighed 600 grams. There were a small patch of old, fibrosed, adhesive pericarditis and some calcification of the aortic valve, with slight stenosis. The other valves were normal. There were no old or fresh infarcts and no fibrosis of the myocardium, grossly. No microscopic sections were made.

Coronary Arteries: The right coronary artery showed a complete, old, calcified occlusion just beyond its origin, and another area of marked narrowing 6.0 cm. beyond this. There were marked atheromatous changes, with narrowing in both

TABLE II

CASES OF CORONARY ARTERIAL OCCLUSION IN WHICH THERE HAD BEEN NO ANGINA PECTORIS

CASE NUMBER	NECROPSY NUMBER	AGE—SEX	HEART WEIGHT GM.	CORONARY ARTERIOSCLEROSIS	CORONARY OCCLUSIONS			MYOCARDIAL FIBROSIS	INFARCTION		CLINICAL CORONARY THROMBOSIS		ETIOLOGY	VALVULAR DISEASE	ANGINA PECTORIS, DURATION	CONGESTIVE FAILURE, DURATION	B. P. ELEVATED	CAUSE OF DEATH
					L. D.	L. C.	R.		OLD	RECENT	PAST	TERMINAL						
a. Cases of Complete Occlusion of at Least One Major Coronary Artery or Primary Branch, Without Infarction																		
13	36-66	75 M	600	+++	0	0	M	0	0	0	0	0	Artscl.	Calcif. A. Sten.	0	2 yr.	+	Cerebral hemorrhage, congestive failure.
14	36-94	62 M	380	++	0	B	0	0	0	0	0	0	Artscl. R. H. D.	Mitral Sten.	0	0	+	Carcinoma stomach—hemorrhage.
15	37-37	66 F	430	+++	M	0	0	+	0	0	0	0	Artscl.	0	0	0	0	Gangrene leg—amputation, postoperative pneumonia.
16	37-117	52 M	360	+++	M, M	M	B	+	0	0	0	0	Artscl.	0	0	0	+	Cerebral hemorrhage.
17	37-127	73 M	440	+++	M, M, B	M, B	0	++	0	0	0	0	Artscl.	0	0	0	0	Rectal abscess, hemorrhage, shock.
18	38-39	54 M	?	+++	0	M	0	+	0	0	0	0	Artscl.	0	0	1½ yr.	+	Congestive failure.
b. Cases in Which There Were Old Infarcts, But No Corresponding History																		
19	37-107	44 M	460	+++	M	0	0	0	+	0	0	+	Artscl.	0	0	0	0	Paroxysmal vent. tachycardia, ?vent. fibrillation.
20	38-81	67 M	490	++	M	M	0	0	+	0	0	0	Artscl.	0	0	0	+	Femoral thrombosis, shock, pulm. edema.

TABLE II CONT'D

c. Cases of Fresh, Ante-mortem Arterial Thrombosis

21	37-2	50 M	430	+	0	(M)	0	0	0	+	0	+	Artscl.	0	0	0	0	Myocardial infarction, ruptured heart.
22	37-15	48 M	400	++	0	0	(M) (M)	+	0	0*	0	+	Artscl.	0	0	0	0	Coronary thrombosis.
23	37-43	70 M	410	+++	0	(M)	M	0	0	+	0	+	Artscl. R. H. D.	Mitral Sten.	0	0	+	Coronary thrombosis, ?vent. standstill or fibrillation.
24	38-17	62 M	440	++	(M)	0	B (B)	0	0	0*	0	0	Artscl.	0	0	0	0	Carcinoma rectum, postoperative shock.
25	38-52	63 M	620	++	0	(M)	0	0	0	+	0	+	Artscl.	0	0	3 yr.	+	?Vent. standstill or fibrillation.

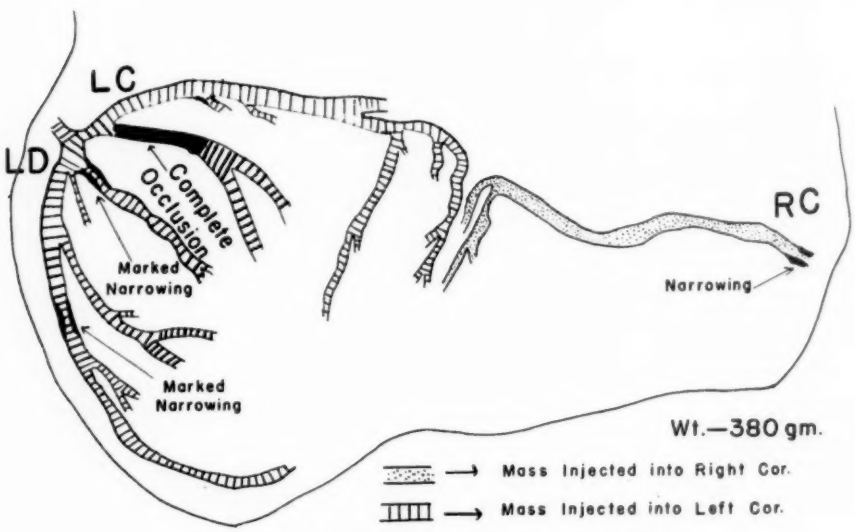
M = Old, complete occlusion of major coronary artery.
(M) = Fresh occlusion of major coronary artery.
B = Old, complete occlusion of primary branch of major coronary artery.
(B) = Fresh occlusion of primary branch of major coronary artery.
Coronary arteriosclerosis + = slight.
++ = moderate.
+++ = marked.
L. D. = Left descending coronary artery.
L. C. = Left circumflex coronary artery.
R. = Right coronary artery.
Calcif. A. Sten. = Calcific aortic stenosis.
R. H. D. = Rheumatic heart disease.
* = Fresh infarct might have developed, had sufficient time elapsed ante-mortem.

the left circumflex and descending coronary arteries, but no points of complete occlusion in these vessels. A rich anastomotic circulation was present in spite of complete occlusion of the right coronary artery and narrowing elsewhere.

Comment.—The absence of angina pectoris is understandable in the light of the previously presented observations, for the tributaries of the right coronary artery were still able to obtain blood through anastomotic channels from both the left anterior descending and left circumflex arteries. The widespread narrowing of all of the main vessels, with consequent generalized interference with adequate blood flow, was evidently responsible for the gradually increasing dyspnea on exertion during the preceding two years and the occurrence of congestive failure during the preceding three months. It is, of course, entirely possible that if the patient's activities had not been limited by dyspnea and weakness, cardiac pain would have occurred. There was no evident cause for the patch of adhesive pericarditis, nor was myocardial fibrosis present in the area beneath the patch. There was no injection of the adherent pericardium by way of penetrating vessels connecting with the coronary circulation from without, such as might have been anticipated from the experimental work of Beck.[2]

CASE 14.—History of cerebral vascular accident four years before death; residual neurologic signs; arterial hypertension; no congestive failure or angina pectoris; death caused by carcinoma of stomach with generalized metastases.

Complete occlusion of one of largest branches of left circumflex artery and narrowing of other coronary branches; anastomotic circulation; no myocardial fibrosis or infarction.



Case 14.—Diagram of coronary arterial tree.

History.—A man, L. M., 62 years old, entered the hospital six weeks before death because of continuous, mild pain in the left shoulder, not related to exertion or emotional disturbances. Four years before death he had suddenly ex-

perienced weakness in the left leg which lasted several days. There was no history of dyspnea or cardiac pain. Physical examination showed a small left pupil, ptosis of the left upper lid, deviation of the tongue to the right, pulling of the mouth to the left, and atrophy of the small muscles of the left hand, forearm, and arm. The heart was enlarged to percussion. There was a soft, systolic murmur, loudest at the aortic area. The blood pressure was 210/96. Serologic tests were negative and the spinal fluid was normal. There was evidence of marked cervical hypertrophic arthritis. The pain gradually disappeared under physiotherapy, and he was discharged improved after twelve days in the hospital. He was readmitted ten days before death, complaining again of pain and weakness in the left arm, and of chest pain, constipation, and distention. The patient was examined repeatedly on the ward services and in the outpatient department. A history of angina pectoris could never be obtained. Physical examination showed cachexia, with signs of fluid at the bases of both lungs and in the abdomen. The liver was palpable four fingerbreadths below the costal margin. Roentgenologic studies revealed evidence of carcinoma of the stomach, with generalized metastases. He died of cachexia and gastrointestinal hemorrhage on the tenth day after admission.

Necropsy.—Heart: The heart weighed 380 grams. There were no old or fresh infarcts, and there was no fibrosis. Several carcinomatous metastases were present in the heart. The valves were normal.

Coronary Arteries: There was only a moderate amount of arteriosclerosis and there were no occlusions of the three major vessels, but there was a complete occlusion of one of the largest branches of the left circumflex artery, with anastomotic injection beyond. This branch was completely occluded and calcified for a distance of approximately 3.0 cm. from its origin. There was some narrowing of the mouth of another smaller branch of the left circumflex artery and also of the distal part of the left anterior descending artery. The mouth of the right coronary artery was narrowed. There was no anastomosis between the right and left coronary circulation.

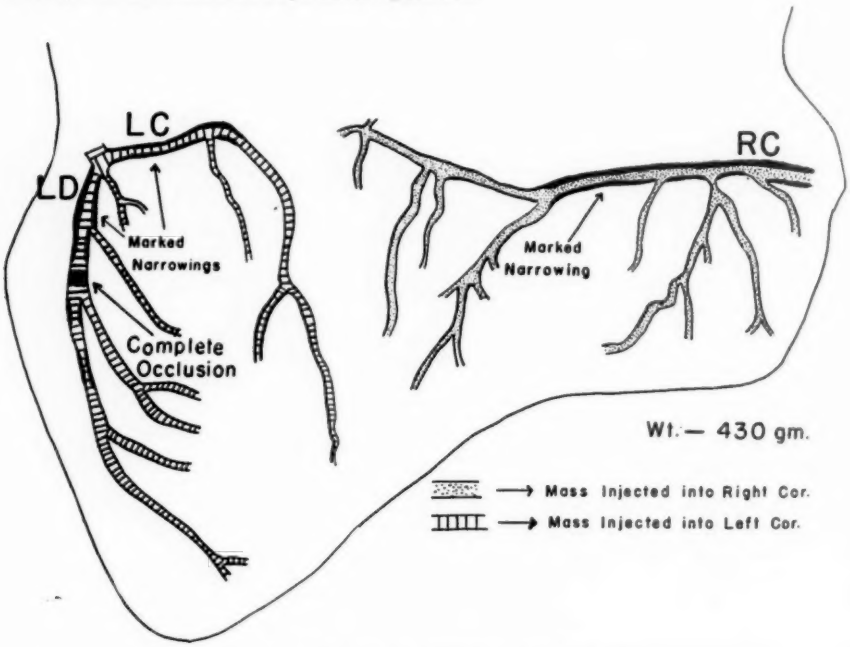
Comment.—The coronary circulation was quite adequate in this heart despite occlusion of one large vessel. This patient, who died of a noncardiac cause, afforded an opportunity to study the earlier stages of coronary arteriosclerosis and the development of a compensating anastomotic circulation which may prevent the occurrence of angina pectoris, diffuse myocardial damage, and congestive failure.

CASE 15.—Diabetes mellitus; no angina pectoris or congestive failure; diabetic gangrene, mid-thigh amputation, death from bronchopneumonia.

All three major coronary arteries showed advanced arteriosclerosis, with narrowing and calcification; old, complete occlusion of left anterior descending artery; rich anastomotic circulation; no myocardial infarction; few small, scattered areas of fibrosis.

History.—A woman, F. F., 66 years old, was admitted to the hospital one week before death because of diabetes and an infection of the left foot. For six years she had been under close medical supervision on the ward service and in the outpatient department for control of her diabetes. There was no history of dyspnea, palpitation, or chest pain at any time in the past. This was corroborated by her physician. The blood pressure had always been approximately 150/80. Physical examination revealed no abnormalities other than a gangrenous infection of the

left foot. The blood pressure was normal. On the fifth day a mid-thigh amputation was performed. During the two days following this her temperature rose to 102° F., her pulse rate to 110, and her respiratory rate to 35. Physical examination revealed signs of bronchopneumonia. Her condition became progressively worse, and she died two days after operation.



Case 15.—Diagram of coronary arterial tree.

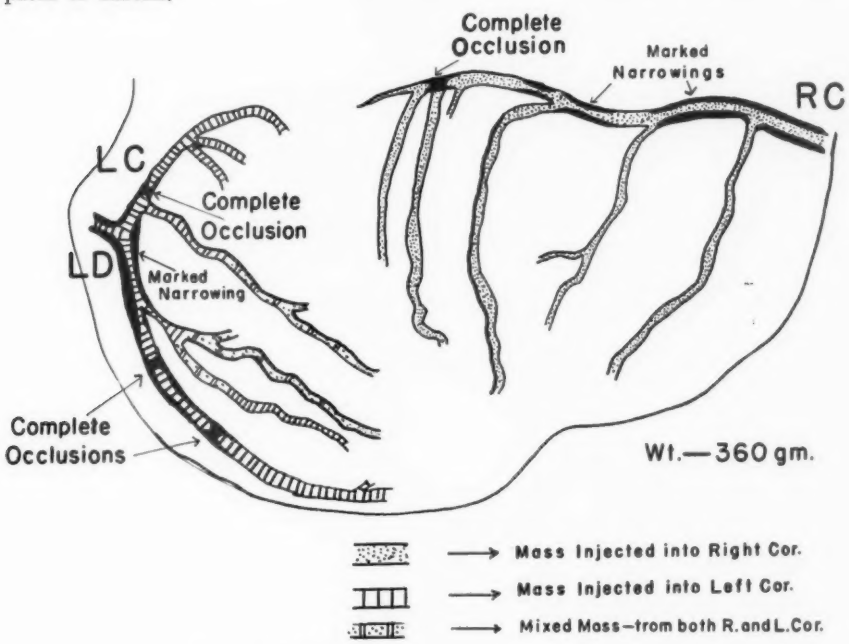
Necropsy.—Heart: The heart weighed 430 grams. There was no old or recent infarct. Only a few, very small, gray, fibrosed patches were found in the myocardium. The mitral valve showed slight stenosis, with calcification, and some shortening and thickening of the chordae tendineae. The other valves were normal.

Coronary Arteries: There was considerable arteriosclerosis, with calcification, throughout all three major coronary arteries. The left circumflex and the right coronary arteries showed considerable narrowing, but were patent and contained injection mass of the same color throughout. The left anterior descending artery showed marked narrowing near its origin, and a point of complete, old occlusion 4.0 cm. from its origin. There was an adequate anastomotic circulation distal to this point and, in general, there was no impairment of the circulation anywhere in the heart.

Comment.—Although this patient had extensive atheromatous changes and complete occlusion of the left anterior descending artery, the area distal to the point of occlusion was apparently adequately supplied through anastomotic channels from the left circumflex artery. It was evident that in this case the anastomotic circulation was sufficient to prevent angina pectoris, whereas other patients with less numerous points of occlusion died, presumably because the occlusions developed too rapidly to permit the development of anastomotic circulation (see below, Cases 21, 22).

CASE 16.—Hypertension for at least one year; no history of angina pectoris or congestive failure; sudden onset of cerebral hemorrhage, with secondary subarachnoid hemorrhage.

Cerebral hemorrhage, secondary softening, and subarachnoid hemorrhage; old, complete occlusions of two main coronary arteries and terminal primary branch of right coronary artery; rich anastomotic circulation; no infarction; occasional tiny patch of fibrosis.



Case 16.—Diagram of coronary arterial tree.

History.—A factory worker, A. G., 52 years old, entered the hospital one month before death. Twenty months previously he had consulted his physician, a member of the hospital staff, because of nervousness and fleeting pains in his joints. He had had rheumatic fever at the age of 20 years. He was a uniform cutter and, despite manual labor, had never experienced cardiac pain or other symptoms suggestive of angina pectoris. He had had occasional palpitation and slight dyspnea during the preceding six months. Physical examination twenty months before admission showed slight enlargement of the heart, a blood pressure of 170/90, slight accentuation of the aortic second sound, and systolic murmurs over the mitral and aortic areas. He was examined again two weeks later and felt markedly improved after the administration of small doses of phenobarbital. He continued at work, felt well, and had not suffered headache or pain at any time until two and one-half weeks before entry, when, while at work, he suddenly became unconscious. He was taken to a relief station, where he was found to have a stiff neck and a bloody spinal fluid. Repeated lumbar punctures showed diminishing amounts of blood; the last one, a few days before admission to the hospital, showed xanthochromic fluid. He had slowly regained consciousness and at the time of admission was completely oriented. Serologic tests were negative. Physical examination showed no dyspnea, cyanosis, or edema. The neck was definitely stiff. He complained of occipital headache. The retinal arteries showed slight atheromatous changes, but there was no retinal hemorrhage or exudate. To

percussion, the heart was slightly enlarged to the left; the heartbeat was slow and regular, the rate 84 per minute, and there was a systolic apical murmur. The blood pressure was 105/70. The diagnosis on admission was subarachnoid hemorrhage and cerebral arteriosclerosis. During the first few days after admission he improved greatly and was about to be discharged, when he again suddenly lost consciousness. The spinal fluid again showed gross blood for several days and then began to clear. He complained of headaches, but was not disoriented. During the third week of his stay in the hospital his condition grew progressively worse, although the spinal fluid was clear. He became incontinent and disoriented. Shortly after this the temperature began to rise, and with the fever there was progressive mental deterioration. On the twenty-first day after admission he developed bronchopneumonia, lapsed into coma, and died on the twenty-eighth day after admission.

Necropsy.—Brain: There was a cerebral hemorrhage, with secondary softening.

Heart: The heart weighed 360 grams. There were no recent or old infarcts. Grossly, the myocardium showed no evidence of fibrosis. Numerous blocks of tissue taken from this heart in all regions, both distal and proximal to the occlusions, revealed merely an occasional, tiny patch of fibrous replacement of muscle. The aortic valve showed some calcification and fusion of the leaflets, but this was not sufficient to cause impairment of function.

Coronary Arteries: There was marked arteriosclerosis, with calcification, throughout the coronary artery tree. Four points of complete, old occlusion were found, two along the main stem of the left anterior descending coronary artery, one near the origin of the left circumflex coronary artery, and one in a terminal primary branch of the right coronary artery. All three major arteries were markedly narrowed near their origins. There was good anastomotic circulation throughout the heart beyond the points of occlusion.

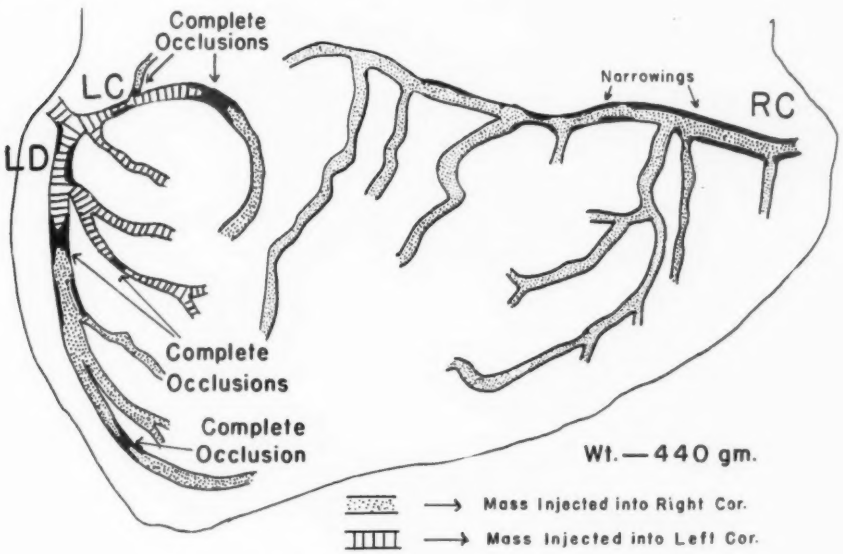
Comment.—This patient with arterial hypertension at no time suffered from angina pectoris or congestive failure, despite old, complete occlusions of two major coronary arteries and of a terminal branch of the third coronary artery; he accomplished his usual work until the onset of the cerebral vascular accident, with subarachnoid hemorrhage. The multiple, complete occlusions had had little effect on the myocardium, judging by the amount of fibrosis, although their locations were such that, collectively, they would have completely cut off the blood supply of the left ventricle if anastomotic connections had not developed as the main stems became occluded. This case illustrates the extraordinary degree to which anastomotic circulation may obviate any serious consequences of complete coronary arterial occlusion, for this patient gave no evidence of cardiac symptoms and showed no areas of significant myocardial fibrosis or of infarction.

CASE 17.—Hospitalization at the age of 73 because of perirectal abscess and urinary retention; no angina pectoris or congestive failure; postoperative hemorrhage, with shock and pulmonary edema.

Extreme coronary arteriosclerosis, with long-standing, complete occlusions of left anterior descending and left circumflex arteries, with unusually large anastomotic communications from the right coronary artery; no fresh or old infarcts; moderate fibrosis.

History.—A man, I. C., 73 years old, was admitted to the hospital eleven days before death, complaining of pain and discomfort in the region of the rectum

and inability to pass urine. He had been under the care of his physician, who had seen him frequently for eight years. His blood pressure had been normal, and he had had no cardiorespiratory symptoms. He had never complained to his physician of dyspnea, or of discomfort or pain in the chest. Physical examination showed a perirectal abscess and a distended urinary bladder. The heartbeat was slow and regular. There were no murmurs. There were a few râles at the bases of both lungs. The blood pressure was 104/90. The abscess was incised and drained under gas-oxygen anesthesia seven days before death. Following this considerable bleeding occurred, and the erythrocyte count dropped to 2,300,000. Two transfusions were given, three and two days before death, respectively, and adequate volumes of fluid were administered. Two days before death, he suddenly became dyspneic and cyanotic and showed marked circulatory collapse. In spite of all treatment he developed numerous râles, which were finally tracheal in character, and expired.



Case 17.—Diagram of coronary arterial tree.

Necropsy.—Heart: The heart weighed 440 grams. There were no definite areas of infarction, fresh or old. However, in a small area in the left ventricle, in the region of the termination of the left circumflex and right coronary arteries, there appeared grossly to be a definite increase in fibrous tissue. Elsewhere the myocardium did not show any gross fibrosis, but microscopic sections showed many small patches of fibrous tissue. In the area mentioned above the fibrosis was especially marked, and was intermingled with areas of normal muscle and also with small patches showing acute necrotic changes accompanied by polymorphonuclear infiltration. The valves were essentially normal.

Coronary Arteries: There was advanced arteriosclerosis, with marked calcification, throughout the major vessels. In spite of this the right coronary artery had a large, patent lumen; it was a large vessel and supplied most of the heart with blood by anastomotic channels. This is a rather unusual occurrence. There were several anastomotic twigs connecting the right and left coronary arteries, and these twigs were larger than usual. The left descending coronary artery showed two points of old, complete occlusion, one near its origin and one distally; there was a similar point of old occlusion in one of its branches. The left circumflex coronary

artery was a rather short vessel and had a point of complete occlusion near its termination. A small branch proximal to this, going to the auricle, was likewise the seat of an old occlusion.

Comment.—In this case there was extreme arteriosclerosis of all three coronary vessels, with long-standing complete occlusions of two main stems, despite which there was no evidence of angina pectoris or congestive failure until operation and subsequent hemorrhage induced terminal shock and pulmonary edema. The relatively uninvolved right coronary vessel and its unusually large anastomotic vessels, which coursed to the left ventricle, were responsible for the maintenance of adequate blood supply.

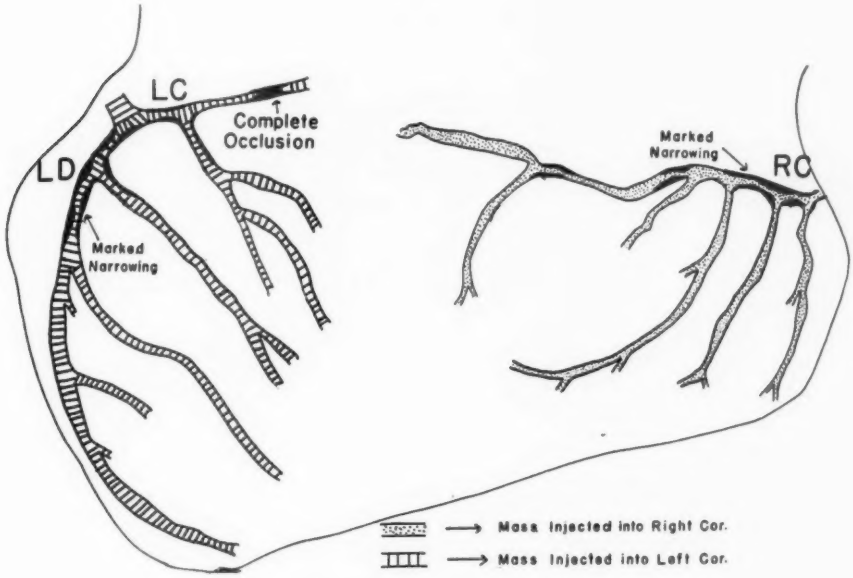
The patches of myocardial necrosis in the localized area of the left ventricle were presumably caused by the increased work and decreased nutrition of the heart consequent to the anemia, infection, and shock. This case illustrates a moderately advanced stage of a mechanism by which massive infarction may be produced in the absence of fresh coronary thrombosis.

CASE 18.—Hypertension, with symptoms, two years; no angina pectoris; congestive failure, one and one-half years.

Distal portion of left circumflex artery occluded; moderate vascular nephritis; no myocardial infarcts; no fibrosis grossly; slight fibrosis microscopically.

History.—A pharmacist, R. S., 54 years old, was first admitted to the hospital one year before death, complaining of dyspnea, fatigue, and edema. He had had "kidney trouble" at the age of 16 years, associated with pyuria for six or seven months. His present illness began one year before entry, when he first noted slight blurring of vision, increasing dizziness, frequent headaches, and fatigue. Approximately seven months before admission, swelling of the feet, palpitation, orthopnea, and dyspnea on exertion prompted him to visit the outpatient department repeatedly. Examination at that time showed extensive eye-ground changes, with hemorrhages, pallor of the discs, and tortuous blood vessels; normal cardiac rhythm; and edema of the legs. The blood pressure was 210/110. The patient had mild diabetes. Repeated urine examinations on various visits to the nephritic clinic showed fixation of specific gravity, traces of albumin, erythrocytes, and, rarely, hyaline casts. Three days before admission to the hospital he complained of paroxysmal nocturnal dyspnea. Physical examination in the hospital showed cyanosis, moderate cardiac enlargement to percussion and roentgenologically, numerous râles at the base of the right lung, and signs of fluid at the base of the left lung. The blood pressure was 170/110. The liver was felt five finger-breadths below the costal margin. There was marked edema of both legs as far up as the thighs. The nonprotein nitrogen content of the blood was 40 mg. per cent, the creatinine 1.5 mg. per cent. An intravenous phenolsulphonephthalein test showed definite impairment of renal function. The electrocardiogram showed left axis deviation, low voltage of the T waves, and slight inversion of T_2. With rest in bed and other appropriate treatment he became free of edema and was discharged three weeks after admission, approximately one year before death. During the next few months edema of the legs recurred, and on several occasions he developed paroxysmal nocturnal dyspnea. He was readmitted to the hospital four months before death, complaining of chilly sensations and a nonproductive cough of a few days' duration. Physical examination showed evidence of ad-

vanced congestive failure and signs suggesting consolidation in the left lung. When he was sufficiently improved, he was transferred to a hospital for chronic diseases. There he did not respond to treatment; edema and anasarca increased rapidly, and he died in congestive heart failure. At no time in the course of his illness did he complain of chest pain.



Case 18.—Diagram of coronary arterial tree.

Necropsy.—Kidneys: Grossly, the kidneys were not unusual. Microscopically, they showed a moderate degree of vascular nephritis.

Heart: The heart was not weighed, but appeared slightly enlarged. Grossly, there were no infarcts, fresh or old, and no gross evidence of fibrosis. Slight fibrosis was evident microscopically. The valves were normal.

Coronary Arteries: The coronary arteries showed marked arteriosclerosis throughout, with much calcification. Narrowing was most marked in the proximal parts of the three major vessels. There was one point of complete occlusion in the extreme distal portion of the left circumflex coronary artery. The small branches distal to this were injected through anastomoses which came entirely from the left coronary artery.

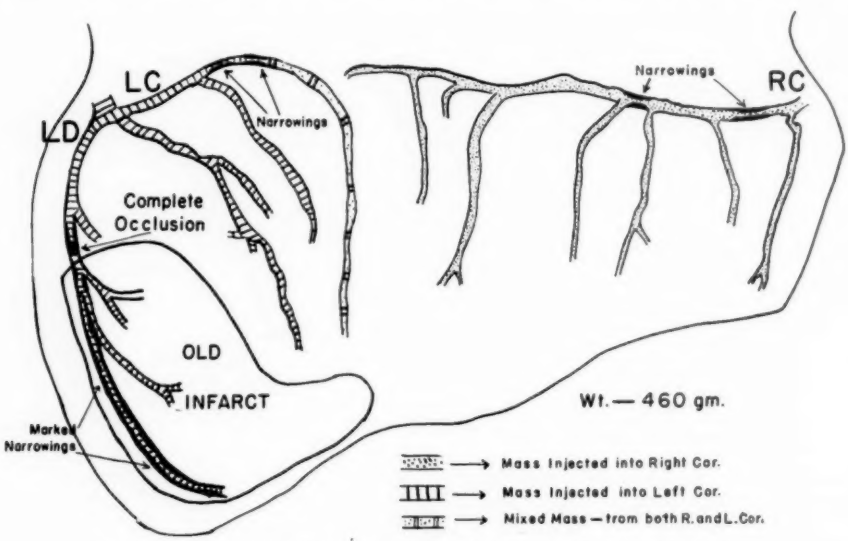
Comment.—This patient did not complain of pain in the chest. He was followed closely in the outpatient department and hospital over a period of two years. There were extensive atherosclerotic changes and narrowings in the proximal portions of the major coronary branches and there was an occlusion at the extreme end of the left circumflex artery. The area beyond this point received anastomotic circulation from the left coronary artery. Anastomotic circulation elsewhere was conspicuously absent. The restricted activity of the patient during the greater part of the final illness might well have prevented angina

pectoris. Throughout the final course of his illness it was difficult to determine how much of the anasarca was due to nephritis and how much to congestive failure. Death, however, was not caused by uremia; there was only a moderate degree of vascular nephritis, and the heart failure was marked. The anatomic basis for the congestive failure was probably a combination of hypertensive hypertrophy and diffuse coronary changes, leading slowly to impaired nutrition.

b. Cases in which there were old infarcts, but no corresponding history

CASE 19.—No history of angina pectoris or congestive failure; cardiac pain, violent palpitation, and collapse, fourteen hours before death; paroxysmal ventricular tachycardia; possible ventricular fibrillation.

Advanced coronary arteriosclerosis, with only slight narrowing of left circumflex and right coronary arteries and old, complete occlusion of left anterior descending artery; old infarct of left ventricle; no diffuse fibrosis; no fresh thrombosis.



Case 19.—Diagram of coronary arterial tree and site of infarct.

History.—A man, J. C., 44 years old, was admitted to the hospital on the day of death, complaining of epigastric pain of nine hours' duration. This patient had been under the close supervision of one of our associates and had been seen repeatedly during the preceding twenty months because of sterility. No cardiorespiratory symptoms had been present at any time. Examination of the heart revealed nothing abnormal. The blood pressure was 110/70. The eye grounds were normal. He had felt perfectly well until the sudden onset of his terminal illness. The pain, originally confined to the epigastrium, later radiated up the sternum and down to the umbilicus and was associated with violent palpitation. When seen by his physician, four hours before admission, he was pale, cyanotic, and pulseless. On admission the pain was referred to the precordium and left shoulder. He was cold, clammy, and cyanotic. The heart was enlarged to percussion, the rate was rapid, and the rhythm normal. An electrocardiogram

showed paroxysmal ventricular tachycardia, with a rate of 220. He was given quinidine without result, and died five hours after admission.

Necropsy.—Heart: The heart weighed 460 grams. There was a large, old, healed, fibrous, partly calcified infarct involving the whole anterior portion of the left ventricle and part of the anterior portion of the interventricular septum. The wall was markedly thinned in this region, and bulged slightly. There was an old, adherent pericarditis over this area. The myocardium elsewhere showed no fibrosis, grossly or microscopically. The valves were entirely normal.

Coronary Arteries: There was marked arteriosclerosis, with calcification, in all three major coronary arteries. This caused areas of only slight narrowing in the left circumflex and right coronary arteries. Shortly after its origin, but distal to the mouth of the main septal artery, the left descending artery was completely occluded and calcified for a distance of about 6.0 mm. Distal to this it was patent, but had only a fine channel. In the infarcted area the vascular bed was reduced considerably as compared with that of the adjacent myocardium. In addition to the anastomotic filling of the left descending artery, there were other anastomotic connections between the left and right coronary arteries. However, but little injection mass could be found in the adherent pericardium over the infarct.

Comment.—This patient, with complete, old obliteration of the lumen of the left anterior descending artery over a distance of 6.0 mm., which had led to infarction, had nevertheless developed sufficient anastomotic circulation from the relatively uninvolved left circumflex and right coronary arteries to sustain life. In the absence of any evidence of fresh thrombosis, death may be attributed to progressive arteriosclerotic involvement, setting up an irritable focus in the ventricular myocardium, with resultant paroxysmal ventricular tachycardia and, probably, ventricular fibrillation. The chest pain was ascribed to the insufficient coronary blood flow and increased work of the heart at a rapid rate of beating. The old infarct may have occurred when little anastomotic circulation was present. In this heart, although there was definite need for it, no extrinsic anastomotic circulation developed through the area of adhesive pericarditis, although it did develop between the various coronary arteries.

Case 20.—No angina pectoris; no congestive heart failure; intermittent claudication; gangrene of left leg; mid-thigh amputation; death caused by pulmonary edema following femoral thrombosis.

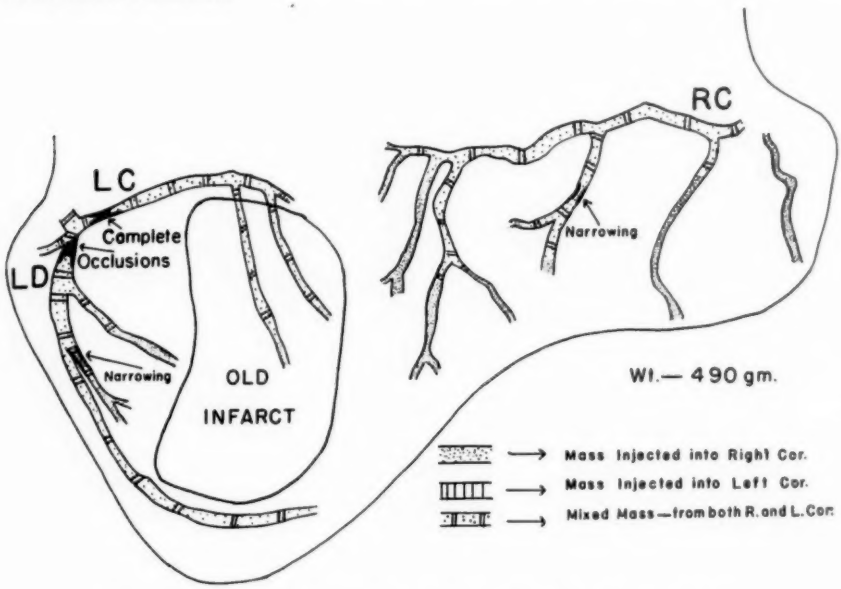
Complete, old occlusions of left anterior descending and circumflex arteries; large, old, fibrosed infarct in posterior half of left ventricle.

History.—A man, E. L., 67 years old, was admitted to the hospital five and one-half months before death, complaining of pain, discoloration, coldness, and weakness in the left leg, of ten days' duration. Six months before, he had noted that exertion caused cramplike pains in both legs which lasted only a few minutes. At this time he also noted occasional swelling in the region of the left ankle, but not elsewhere. At no time did he experience precordial or chest pain, palpitation, orthopnea, or shortness of breath, and, according to two independently elicited histories, he could climb three flights of stairs slowly, without discomfort, prior to several weeks before admission.

Physical examination showed evidences of generalized arteriosclerosis, a slow heart rate, normal cardiac rhythm, pulmonary emphysema, no abnormality of the lungs, an irreducible right scrotal hernia, and gangrene of the left lower ex-

tremity, which was totally devoid of circulation beginning two inches below the knee. The blood pressure was 148/72. A left mid-thigh amputation was performed under spinal anesthesia on the day of admission. The patient lapsed into shock and unconsciousness on the operating table, but recovered the same afternoon. Thereafter the convalescence was uneventful, and he was discharged four weeks after admission.

Four and one-half months later he was readmitted; he had pulmonary edema, and was complaining of continuous pain in the right calf, which was cramplike in nature. The pulse rate was 120. The blood pressure was 210/170. The femoral, popliteal, and dorsalis pedis pulsations were absent. Tourniquets were applied, and morphine was given, with some relief, but he expired suddenly a few hours after admission.



Case 20.—Diagram of coronary arterial tree and site of infarct.

Necropsy.—Heart: The heart weighed 490 grams. A large, old, fibrosed infarct occupied most of the posterior half of the left ventricle. This infarct was partly calcified. The infarcted area was well vascularized. Elsewhere, the myocardium did not appear grossly fibrosed. There was no recent infarct. The valves were essentially normal.

Coronary Arteries: The coronary arteries showed only a moderate degree of generalized arteriosclerosis. However, there were complete occlusions just distal to the origins of both the left descending and left circumflex coronary arteries. There was an additional point of marked narrowing in one branch of the left descending coronary artery. The right coronary artery showed no occlusions. The only large branch coming from the left coronary artery, proximal to the two points of occlusion, was a rather large septal vessel. There were no fresh thrombi in any of the coronaries. There was a rich anastomotic circulation throughout the coronary tree, which was intact distal to the occluded points.

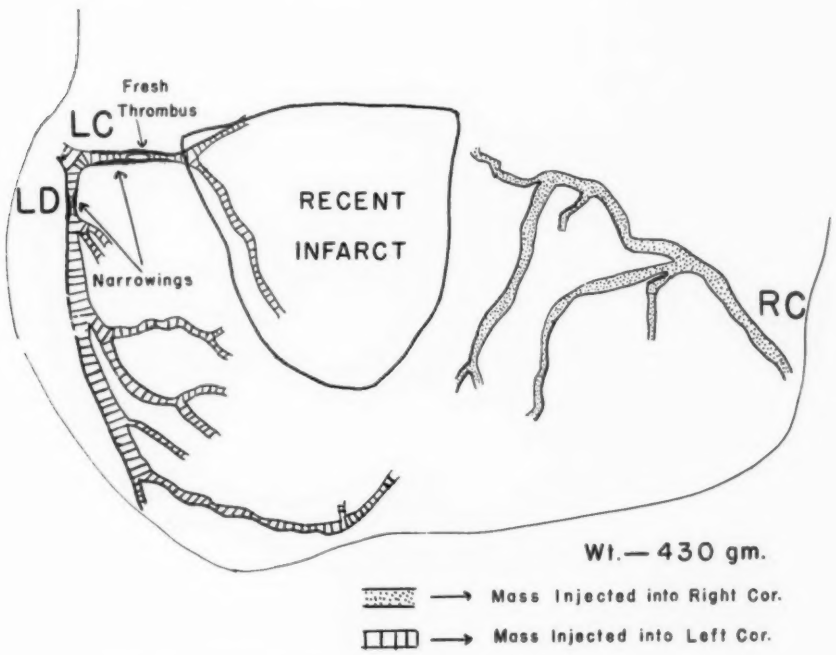
Comment.—This patient, despite the presence of a large, healed infarct involving most of the posterior half of the left ventricle, and old occlusions near the origins of the left descending and left circum-

flex arteries, gave no history and showed no evidence of congestive failure or angina pectoris. It is impossible to dismiss the possibility that a history of precordial pain or distress would have been elicited at some time, had he been under continuous observation, but it is nevertheless remarkable that, with such an extensive infarct in the left ventricle and complete occlusions of both left coronary arteries, neither frank congestive failure nor obvious heart pains were present. The injection and dissection studies showed that the remainder of the coronary tree was only moderately involved, permitting the development of a rich anastomotic circulation throughout, with good injection beyond the areas of vascular occlusion. The intermittent claudication and subsequent gangrene prevented the patient from undertaking degrees of exertion which might have induced angina pectoris or congestive failure.

c. Cases of fresh ante-mortem arterial thrombosis

CASE 21.—Close supervision for nine years because of gastrointestinal complaints. Paroxysmal auricular tachycardia, four years; no congestive failure; angina pectoris, eleven days; coronary thrombosis, myocardial infarction, and death.

Narrowing of left anterior descending and left circumflex arteries; freshly deposited thrombus completely occluding left circumflex artery; myocardial infarction and subsequent rupture of the heart.



Case 21.—Diagram of coronary arterial tree and site of infarct.

History.—A man, W. G., 50 years old, was a department head in the hospital who had been under continual, close medical supervision for nine years before death. He had been admitted to the hospital eight years before death because of recurrent

pain in the right lower quadrant, suggestive of appendicitis. Physical examination of the heart showed nothing abnormal. The blood pressure was 130/84. Five years before death he was again studied because of epigastric distress and tenderness during the preceding six months. This distress usually occurred after dinner, following a hard day's work or a day of excitement, lasted one and one-half hours, and was relieved within a half hour by soda. Physical examination showed normal cardiac mechanism; the blood pressure was 132/62; and there was slight tenderness in the epigastrium. Roentgenologic examination of the gastrointestinal tract and gall bladder showed nothing abnormal. Beginning four years before death, he noted attacks of paroxysmal tachycardia, and was admitted to the hospital three years before death because of an attack which had persisted since the preceding evening, when he had been shoveling snow. The electrocardiogram showed tachycardia of auricular origin. The rate was 187 and the beating absolutely regular. The heart rate and electrocardiogram returned to normal after quinidine therapy. He continued to have abdominal distress and headache, but despite fairly heavy work and emotional tension he at no time showed anything suggestive of angina pectoris. Following each attack of tachycardia he was examined for evidence of cardiac disease, but none was found. Eleven days before death he began to have attacks of substernal pain, associated with dyspnea, and induced by mild exertion, exposure to cold, and excitement, but relieved by nitroglycerin. On the morning of admission, six days before death, he experienced persistent, excruciating substernal pain, radiating down the left arm. Physical examination was essentially negative. The heartbeat was slow and regular. The leucocyte count was 6,900. The temperature rose to 102° F. on the day following admission and remained elevated until death. The blood pressure remained between 110/80 and 130/90. The pain gradually subsided, and he was feeling better, when he suddenly became ashen, dyspneic, and expired.

Necropsy.—Heart: The heart weighed 430 grams. In the posterior portion of the left ventricle, near the base, in the region supplied by the left circumflex artery, there was a large, fresh infarct. At the anterior border of the infarct there was a tear of the myocardium 1.0 cm. long. The infarcted region was not quite bloodless. There was no diffuse fibrosis. The valves were normal.

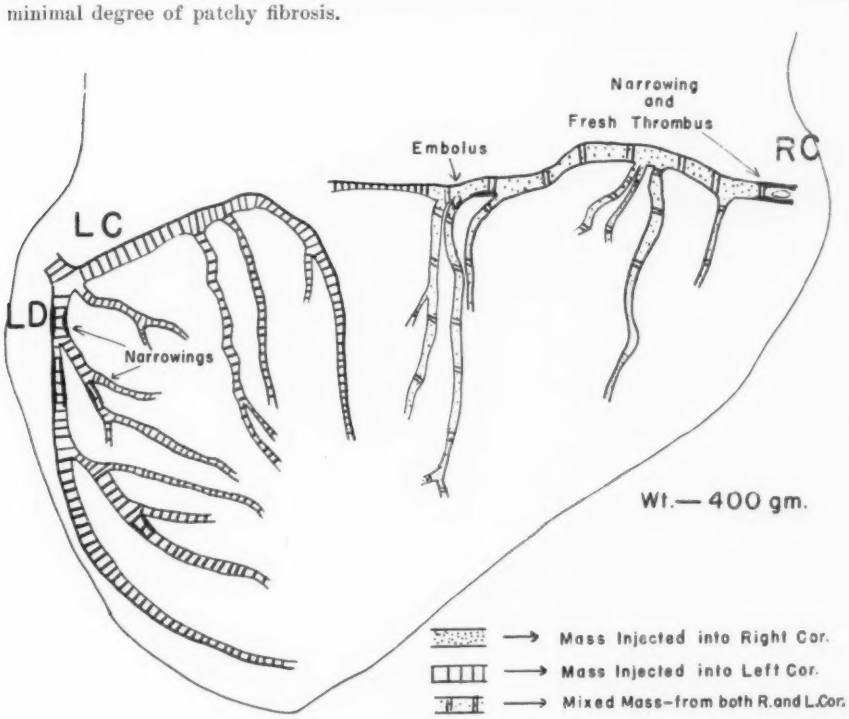
Coronary Arteries: The right coronary artery was absolutely normal; the left anterior descending coronary artery was narrowed near its origin. There was an extensive area of arteriosclerosis, with considerable narrowing, but no calcification, near the origin of the left circumflex artery. Deposited on this plaque was a large occluding thrombus. The arterial tree distal to the freshly occluded portion of the left circumflex artery, that is, in the region of the fresh infarct, was only poorly filled by material injected into the left coronary artery. There was no anastomotic communication with the right coronary artery.

Comment.—This patient had atheromatous changes confined to the left circumflex and anterior descending arteries. He had had no symptoms of angina pectoris, despite heavy exertion and emotional strain, until eleven days before death. He had been under particularly close medical supervision and had been questioned frequently for nine years. The considerable narrowing of the left circumflex artery had led to the development of some anastomotic circulation from the left coronary artery. This compensatory anastomotic circulation was sufficient to prevent angina pectoris. It was, however, insufficient to withstand the final, sudden, complete, thrombotic occlusion of the left circumflex artery which led to the development of attacks of angina pectoris, the clinical and pathologic evidences of cardiac infarction, and, finally,

rupture of the heart. Had this occlusion of the left circumflex artery developed more slowly, or had the patient avoided the strain of work during the five days preceding hospital admission, it is possible that a more extensive anastomotic circulation would have developed and that infarction might not have resulted. In other cases, complete occlusion of even two of the three main arteries occasioned no symptoms of angina pectoris and no pathologic evidence of cardiac infarction. This case exemplifies the importance of the speed with which narrowing of a vessel and occlusion of its lumen develop; if partial, as in the earlier part of this patient's course, no myocardial damage and no symptoms result; if a large vessel is suddenly occluded, as in the final stages of the illness in this case, when thrombosis occurred, myocardial infarction and death may occur.

CASE 22.—No angina pectoris or congestive failure until three days before death; sudden onset of severe, persistent, substernal pressure; coronary thrombosis and death.

Narrowing of left descending and right coronary arteries; fresh thrombus occluding right coronary; secondary embolus from this thrombus occluding terminal end of this artery; adequate anastomotic circulation before terminal thrombosis; minimal degree of patchy fibrosis.



Case 22.—Diagram of coronary arterial tree.

History.—A man, G. S., 48 years old, had been observed repeatedly by a physician on the hospital staff, from whom an especially careful history was obtained. The patient had felt well and had not experienced pain in the chest or

dyspnea until three days before death, when he suddenly developed a severe, substernal, pressing pain which persisted for twelve hours. He nevertheless worked at his office on this and the following days. On the third day, beginning at 5:00 P.M., continuous substernal pain recurred and radiated to both arms, and after five hours became extremely severe. When seen by his physician the patient showed the syndrome of coronary thrombosis, with normal cardiac rhythm and circulatory collapse, and expired a few hours later.

Necropsy.—Heart: The heart weighed 400 grams. There were no old or fresh infarcts recognizable grossly, and the microscopic sections showed no area of fresh infarction. Only a minimal degree of patchy fibrosis was present in the myocardium. The valves were normal.

Coronary Arteries: There was narrowing of the left descending and right coronary arteries, none of the left circumflex artery. In the right coronary artery, near its mouth, there was a fresh thrombus, 0.7 cm. in length, which had been deposited on an ulcerated atheromatous plaque. The fresh thrombus practically completely occluded the lumen. At the distal end of this same vessel there was a mushroom-shaped embolus, lightly adherent to the vessel wall, its stem plugging one of the larger branches that supplied the area of the bundle of His. This embolus undoubtedly came from the thrombus at the mouth of the right coronary artery. There was apparently an adequate anastomotic circulation from the left coronary artery beyond these two fresh obstructions on the right side, for the branches of the right coronary were all well injected with a mixed mass which came partly from the right and partly from the left arteries.

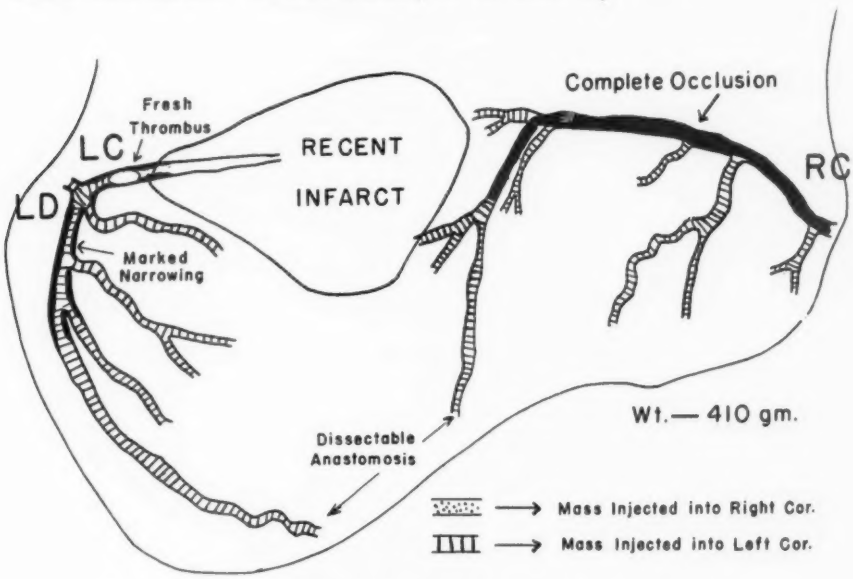
Comment.—This patient showed only slight to moderate atheromatous changes throughout the coronary tree, and there were no old occlusions. Death was caused by the formation of a fresh thrombus in an atheromatous ulcer. The patient might have survived, had this thrombus not released an embolus to the distal part of the coronary artery. The onset of the first pain, which did not prevent the patient from going to work, was probably the result of the formation of the fresh thrombus; had he been at complete rest, embolism might not have occurred. The embolus in the terminal branch naturally reduced the anastomotic circulation from the left coronary vessels. The fact that the plugged vessel led to the A-V bundle must also be taken into account in considering the mechanism of death. If the patient had survived, it is probable that he would have shown evidence of infarction in spite of the presence of some collateral circulation.

Prior to the terminal thrombotic occlusion of the right coronary, the absence of angina pectoris was consistent with the fact that all of the major coronary arteries were patent, and that there was an anastomotic circulation which compensated for the narrowing of the lumina of the left descending and right arteries.

CASE 23.—No angina pectoris or congestive failure until terminal illness; arterial hypertension; coronary thrombosis and collapse.

Entire right coronary artery obliterated by old arteriosclerotic process; left anterior descending markedly narrowed but not completely occluded; left circumflex arteriosclerotic, with fresh thrombosis and no injection distally; rich anastomotic circulation; fresh infarct; calcified mitral valve.

History.—A man, B. M., 70 years old, was admitted to the hospital nine days before death with a history of sudden onset, three days before entry, of severe pain, while up and about, in the interscapular region. He was seen soon thereafter by his physician, who did not recognize the gravity of his condition and permitted him to be ambulatory. Three days later, because of increased intensity of pain, the patient visited another physician, who found evidence of congestion at the bases of both lungs and immediately brought him to the hospital. Close questioning revealed no history of palpitation, dyspnea, or pain in the chest prior to this illness. The blood pressure at this time was 205/105. The interscapular pain was now associated with epigastric and substernal pain, and persisted until the time of admission. On admission to the hospital, no history of other cardiac symptoms was elicited. Physical examination showed acute distress, dyspnea, orthopnea, and cyanosis. The heartbeat was regular, the rate 115. At the bases of the lungs there were dullness and crepitant râles. The blood pressure was 170/60. An electrocardiogram showed a prolonged P-R interval, an elevated S-T interval in Lead IV, and absence of Q_4 (old nomenclature). Successive electrocardiograms in the next few days showed the development of diphasic T waves in all leads. On the third day after his admission, the signs of pulmonary involvement increased, and there was a rise in temperature to 102° F. On the seventh and eighth days two attacks of severe chest pain occurred, and dyspnea and cyanosis became more marked. He died suddenly on the ninth day.



Case 23.—Diagram of coronary arterial tree and site of infarct.

Necropsy.—Heart: The heart weighed 410 grams. There was a large area of infarction, measuring about 8.0 cm. in diameter, in the posterior portion of the left ventricle, near the base. This area of infarction also involved the adjacent interventricular septum and extended into the adjacent auricle. This was a recent infarct which presented the picture of marked necrosis in the medial zone of the musculature; the subendocardial and subepicardial zones were less involved. There was no intraventricular thrombosis overlying the infarct. The mitral valve showed slight stenosis, with thickening of the leaflets, calcification of the ring, and shortening of the chordae tendineae. The other valves were es-

sentially normal. Microscopically, the myocardium showed no old, diffuse fibrosis, and the infarcted area showed a very intimate and irregular admixture of patches of completely necrotic muscle fibers and well-preserved fibers.

Coronary Arteries: There was much arteriosclerosis throughout the coronary arterial tree. The left anterior descending coronary artery was markedly narrowed, but nowhere completely occluded. The lumen of the right coronary artery was completely obliterated by an old arteriosclerotic process, extending from a point close to its origin to a point well down on the posterior interventricular sulcus. Distal to this occluded zone its lumen was again open and large, and it anastomosed, by means of a large, dissectible vessel, with the termination of the left descending coronary artery, a very unusual occurrence. The left circumflex artery was greatly narrowed, and a recently deposited, partly broken-down thrombus was found near its origin. Only a few of the branches of this artery, including the auricular arteries, distal to this thrombosis were injected through anastomotic connections. This almost bloodless zone comprised the infarcted area, which extended to the auricle. In contrast, the branches of the occluded right coronary artery were well injected through the left coronary arterial anastomotic connections.

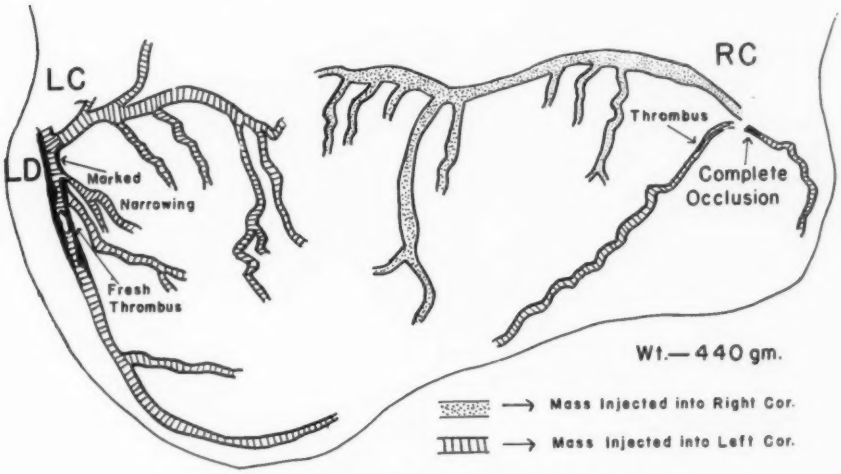
Comment.—Before the final illness this patient had had obliteration of the entire right coronary artery and narrowing of the left anterior descending artery, conditions usually considered as predisposing to ischemia and the development of angina pectoris. However, the patient did not have angina pectoris, and death was caused by myocardial infarction which resulted from the formation of a fresh thrombus in the left circumflex artery. This case shows to an extraordinary degree the extent to which anastomotic circulation may compensate for defects in the major arteries. Since the right coronary was entirely obliterated, and the left anterior descending artery was greatly narrowed, the circulation to a considerable part of the heart must have depended on anastomotic vessels from the left circumflex artery, as well as from the left anterior descending artery. Thrombosis of the left circumflex artery consequently resulted in death. There was no injection mass distal to the thrombotic occlusion. Acute thrombosis of only the left anterior descending artery would probably have been fatal also, for injection disclosed that the unusually large vessel representing a continuation of the left anterior descending artery nourished that part of the heart usually supplied by the right coronary artery.

Case 24.—No angina pectoris or congestive failure; rectal carcinoma, with secondary perirectal abscess; death caused by generalized metastases. Postoperative shock, generalized peritonitis, and terminal bronchopneumonia.

Moderate coronary arteriosclerosis; marked narrowing at two places in the anterior descending artery; old occlusion in a small branch of right coronary artery; fresh thrombus in anterior descending artery, and also in branch of right coronary artery.

History.—A man, W. V., 62 years old, was admitted to the hospital nineteen days before death because of a perirectal abscess secondary to carcinoma of the rectum, which had caused local symptoms during the preceding four years. The past history was negative for dyspnea or pain in the chest. Physical examination

disclosed nothing remarkable. Examination of the heart showed nothing abnormal. The blood pressure was 120/76. A colostomy was performed in two stages. Following the second-stage operation, the patient suddenly became cold, clammy, and semicomatose; the pulse was rapid and thready, and the blood pressure fell. A roentgenogram revealed a large amount of air under the diaphragm. The patient developed generalized peritonitis and bronchopneumonia and died the following day.



Case 24.—Diagram of coronary arterial tree.

Necropsy.—Heart: The heart weighed 440 grams. There were no old or recent infarcts, and the myocardium showed no fibrosis, grossly or microscopically. The valves were essentially normal.

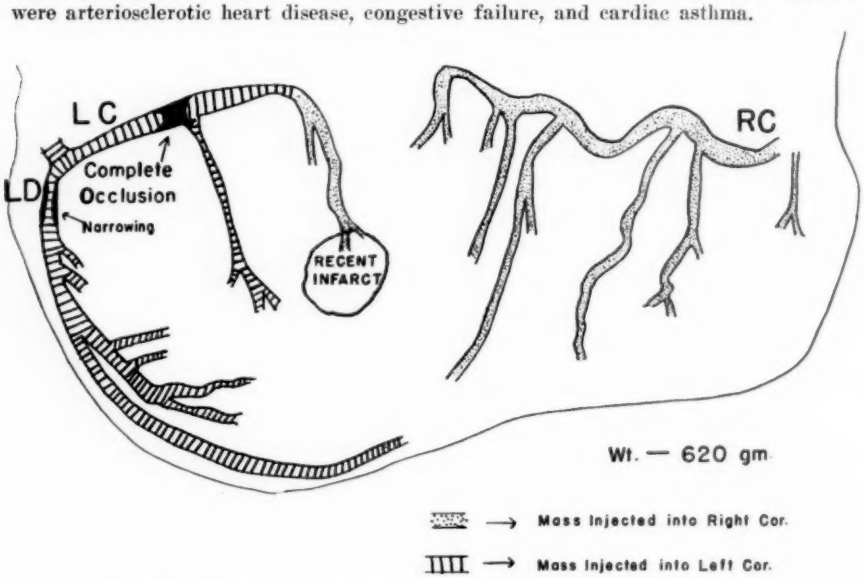
Coronary Arteries: There was only moderate arteriosclerosis throughout the coronary arteries. However, in two spots this was marked. The first centimeter and a half of the left anterior descending coronary artery showed pronounced arteriosclerosis, with calcification and marked narrowing of the lumen. This lumen was finally completely occluded by a string-like, fresh thrombus. Distal to this fresh occlusion, which was on the site of an area of old, extreme narrowing, the vessel and its branches were well injected through an anastomotic circulation. The main stem of the right coronary artery had an adequate lumen. A small branch of the right coronary artery was completely closed off by an old occlusion, and another small branch nearby contained a freshly deposited thrombus. Both of these branches were filled by way of anastomotic vessels from the left coronary.

Comment.—The presence of two independently formed, fresh, antemortem thrombi suggests that, as in Case 11, shock consequent to infection, malignancy, operations, or hemorrhage predisposes to the formation of thrombotic occlusions. It is possible that, had the patient lived, these terminal occlusions of markedly narrowed arteries would not have given rise to infarction because of the adequacy of the anastomotic circulation which had already developed through the stimulus of a greatly narrowed left anterior descending artery.

Case 25.—Arterial hypertension; no angina pectoris; congestive failure, three years; repeated attacks of severe cardiac asthma; attack of substernal pain, one month before death; sudden death; questionable ventricular fibrillation.

Occlusion of left circumflex artery and healing infarct of the left ventricle.

History.—J. A., a man, 63 years old, was first admitted to the hospital ten years before death for treatment of a right inguinal hernia. At that time he gave no history of chest pain or dyspnea. The blood pressure was 130/80. On his second admission, twenty-three months before death, he complained of progressive weakness and dyspnea of nine months' duration. Despite rest in bed from time to time, and digitalis, he had developed a severe cough productive of whitish sputum, and two days before this admission was awakened at 3:00 A.M. by a severe attack of paroxysmal nocturnal dyspnea which persisted for two hours. He had been closely observed by one of our associates, who had repeatedly found that the blood pressure was 190/90 when the patient was up and about. Physical examination on entry showed cardiac enlargement, normal cardiac rhythm interrupted by premature beats, and moist and musical râles all over both lungs posteriorly, particularly at the bases. The edge of the liver was three fingerbreadths below the costal margin. The blood pressure was 140/90. The vital capacity was 1,500 c.c. A teleoroentgenogram showed definite cardiac enlargement to the left and downward, with a transverse cardiac diameter of 16.0 cm. and an internal chest diameter of 30.5 cm. The electrocardiogram showed flat T waves in Leads I, II, and III; P_1 was notched. The administration of salyrgan was followed by diuresis, and the signs and symptoms of congestive failure quickly disappeared except for râles at the bases of both lungs, which persisted throughout his fourteen-day stay in the hospital. The diagnoses were arteriosclerotic heart disease, congestive failure, and cardiac asthma.



Case 25.—Diagram of coronary arterial tree and site of infarct.

He was again admitted one month later, twenty-one months before death, because of recurrence of symptoms and a severe attack of cardiac asthma on the night before admission. The physical findings were essentially the same as on his previous admission. The administration of mercurial diuretics was followed by a loss of ten pounds in the first three days, and disappearance of the signs of congestive failure. He was discharged improved after twenty-four days.

After this he limited his activities greatly. During the interval of almost two years until his final admission, eighteen days before death, he was symptom-free except for attacks of a choking sensation at night which occurred approximately once every three or four months. At midnight, just before admission, he was

awakened by a severe, squeezing pain in the upper substernal region which was somewhat relieved by morphine, but again became increasingly intense toward morning. Physical examination on admission showed a grossly irregular and rapid heart beat, with an appreciable pulse deficit, a moderate number of crackling râles at the bases of both lungs, and a blood pressure of 110/70. On the day after admission the heart beat became regular, and he was more comfortable. The electrocardiogram showed a markedly depressed S-T_4 and numerous ventricular systoles from different foci. During the next eighteen days in the hospital his temperature fluctuated between 101° and 103° F. Signs of congestive failure then disappeared, and the temperature became normal. No friction rub was heard at any time. There were persistent crackling and musical râles at the bases of both lungs. On the twenty-fifth hospital day, without premonitory symptoms, he suddenly stopped breathing, became very cyanotic, and expired within two minutes.

Necropsy.—Heart: The heart weighed 620 grams. A fresh, sterile, serofibrinous pericarditis was present. There was an infarct of the left ventricle, near its base posteriorly, almost healed, but not yet replaced by a fibrous scar. Fibrosis was not noted elsewhere in the myocardium. There were no valvular lesions.

Coronary Arteries: There was only a moderate degree of arteriosclerosis, confined entirely to the left coronary artery. The right coronary artery was normal. The left descending coronary artery showed arteriosclerotic narrowing near its origin, but no occlusion. An old occlusion was present midway along the left circumflex coronary artery, and the infarcted area was presumably related to this occlusion. Beyond this occlusion there was some anastomotic circulation both from the right and left coronary arteries. There were no fresh thrombi in any of the vessels.

Comment.—This case is of interest because, although there was definite evidence of myocardial insufficiency, as shown by the congestive failure, repeated attacks of cardiac asthma, and a greatly hypertrophied heart, the coronary arterial tree showed only moderate arteriosclerotic changes. This suggests that in the presence of marked hypertrophy, with its attendant increased circulatory needs, even moderate interference with blood flow may have serious consequences, particularly when increased work of the heart is necessary because of arterial hypertension. Prior to the occurrence of occlusion of the left circumflex artery one month before death, narrowing of the left anterior descending, and probably of the left circumflex, had led to the development of some anastomotic circulation, arising from the right coronary artery. When occlusion of the left circumflex artery occurred, sufficient anastomotic circulation was present to prevent death, even though infarction took place. During the succeeding month in the hospital the signs of congestive failure had almost disappeared, and the patient was making an uneventful recovery at the time of his sudden death. The presence of numerous ventricular extrasystoles from different foci suggests that certain areas were irritable because of persistent anoxemia; death was possibly caused by the sudden development of ventricular fibrillation.

3. CASES OF ANGINA PECTORIS WITH PRECEDING CONGESTIVE HEART FAILURE OR WITH VALVULAR DISEASE - - - - - - - - - - (TABLE III)

Table III

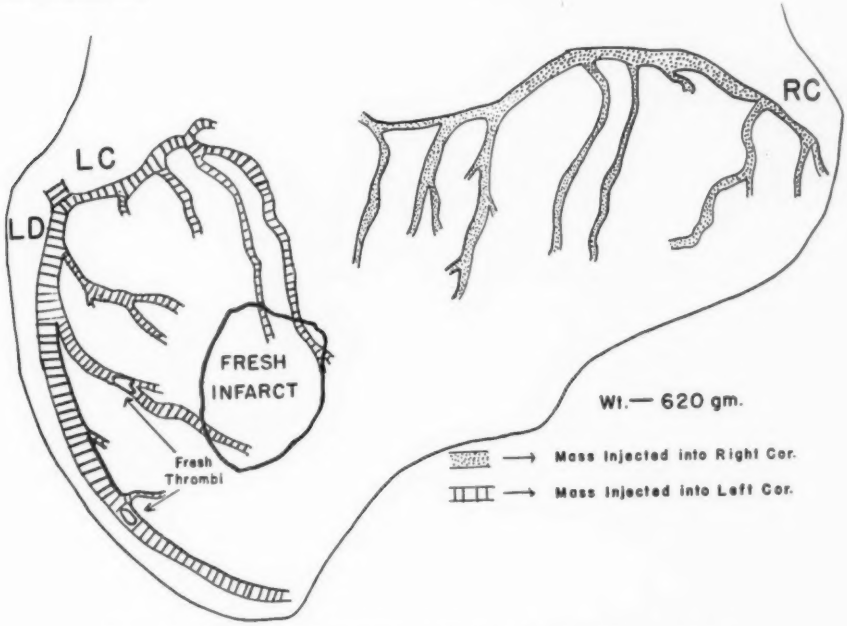
Cases of Angina Pectoris With Preceding Congestive Heart Failure or With Valvular Disease

Case Number	Necropsy Number	Age—Sex	Heart Weight Gm.	Coronary Arterio-sclerosis	Coronary Occlusions			Myocardial Fibrosis	Infarction		Clinical Coronary Throm-bosis		Etiology Cardiac Dis.	Valve Involved	Angina Pectoris, Duration	Congestive Failure, Duration	B. P. Elevated	Cause of Death
					L. D.	L. C.	R.		Old	Recent	Past	Terminal						
26	37-59	68 M	620	+	(M) (B)	0	0	0	0	+	0	0	R. H. D. Hyperten.	Mitral	11 yr.	11 yr.	+	Congestive failure
27	38-2	26 M	1380	0	0	0	0	0	0	0	0	0	R. H. D.	Aortic	5 yr.	10 yr.	+	Congestive failure
28	37-100	51 M	620	+++	0	0	0	+	+	0	+	0	R. H. D.	Aortic, Mitral	6 yr.	* 3 yr.	0	Pulmonary infarction
29	37-83	60 M	460	+	0	0	0	0	0	0	0	0	Cor pulm.	0	6 wk.	2 yr.	0	Congestive failure
30	38-82	55 M	?	+++	M	0	0	+	+	0	+	0	Artscl.	0	1 yr.	2 yr.	0	Cerebral hemorrhage

M = Old, complete occlusion of major coronary artery.
(M) = Fresh occlusion of major coronary artery.
B = Old, complete occlusion of primary branch of major coronary artery.
(B) = Fresh occlusion of primary branch of major coronary artery.
Coronary arteriosclerosis + = slight.
++ = moderate.
+++ = marked.
L. D. = Left descending coronary artery.
L. C. = Left circumflex coronary artery.
R. = Right coronary artery.
R. H. D. = Rheumatic heart disease.
Hyperten. = Arterial hypertension.
Cor Pulm. = Cor pulmonale.
* = Paroxysmal nocturnal dyspnea.

CASE 26.—Arterial hypertension, twelve years; angina pectoris, dyspnea, and palpitation, eleven years; rheumatic heart disease; mitral stenosis and insufficiency; cardiac enlargement; increasing congestive failure and death.

Fresh coronary thrombosis of main left anterior descending artery and also of one of its large branches; fresh myocardial infarction; slight, scattered, coronary arteriosclerosis.



Case 26.—Diagram of coronary arterial tree and site of infarct.

History.—A man, M. G., 68 years of age, was admitted to the hospital eight days before death because of cardiac pain and evidences of congestive failure. Arterial hypertension had been present for twelve years; precordial pain which was relieved by nitroglycerin and precipitated by exertion, emotion, and cold had been noted for eleven years, and dyspnea and palpitation on exertion during the same time. Four years previously, he had spent five weeks in the hospital because of increasing dyspnea, increasing frequency and intensity of the pain, and one severe attack which had lasted one and one-half hours. Physical examination at that time had disclosed cardiac enlargement to percussion, a systolic and mid-diastolic rumbling murmur at the mitral area, and râles at the bases of both lungs. The liver was not enlarged, and there was no edema. The blood pressure was 180/100. A teleoroentgenogram showed a transverse cardiac diameter of 17.2 cm. and an internal chest diameter of 31.1 cm. The electrocardiogram showed slight left axis deviation and a depressed S-T interval in Lead IV, but was otherwise normal. Subsequent electrocardiograms revealed no further changes. He was discharged from the hospital at the end of five weeks, much improved. The diagnoses were angina pectoris, arterial hypertension, cardiac enlargement, and mitral stenosis and insufficiency.

After discharge from the hospital he restricted his activities; the attacks of angina pectoris continued, but, beginning one and one-half years before death, became much less frequent and severe. Beginning seventeen days before death he suffered several attacks of paroxysmal nocturnal dyspnea and complained of nausea and cough. On admission to the hospital, eight days before death, cyanosis, dyspnea, orthopnea, and dullness and râles at the bases of both lungs were observed. The

heart was enlarged and the rate rapid. The blood pressure was 260/150. Electrocardiograms showed auricular flutter, with an auricular rate of 374 and a ventricular rate of 187. The edge of the liver was palpable three fingerbreadths below the right costal margin. The administration of adequate doses of digitalis converted the flutter to auricular fibrillation, with a slow ventricular rate. Despite this, the congestive failure increased progressively, and on the eighth hospital day, while the cardiac and radial pulse rates were being counted, his heart suddenly stopped; after a few gasping respirations, he died.

Necropsy.—Heart: The heart weighed 620 grams. The left ventricle was hypertrophied. Along the lateral border of the left ventricle, near the obtuse margin, there was an ill-defined area of slight softening and discoloration of the myocardium, suggesting early infarction. There were no other areas of old or fresh infarction, nor was there any diffuse fibrosis of the myocardium. The mitral valve was stenosed and calcified. The other valves were not unusual.

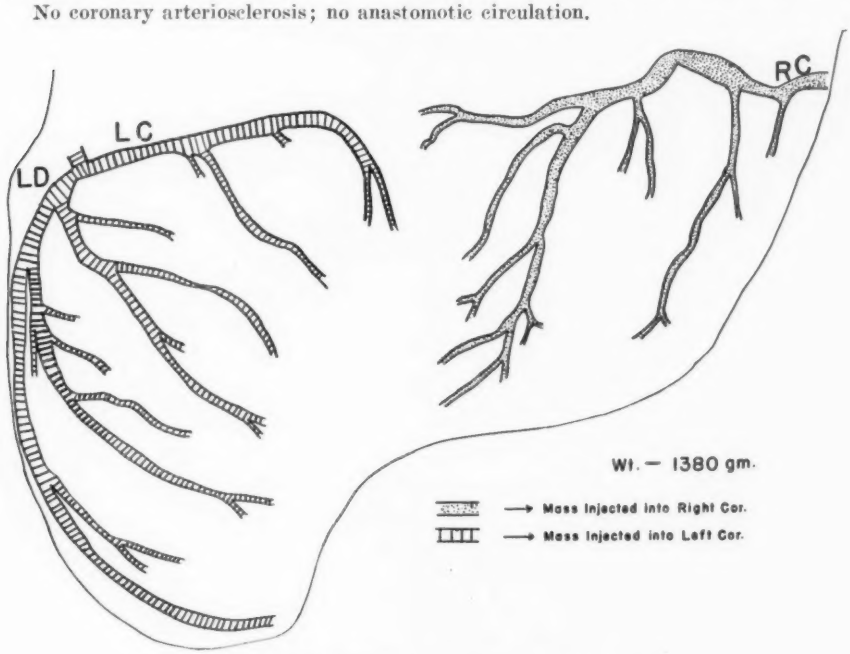
Coronary Arteries: The coronary arteries showed only a small amount of scattered atherosclerosis, without narrowing. However, in the left descending coronary artery, well down near the apex, on an atheromatous plaque, there was a fresh thrombus which almost occluded the lumen. A large branch of this artery above this point was completely occluded by a freshly deposited thrombus. Both of these vessels were going in the direction of the area in the left ventricle in which, grossly, early infarction seemed to be present. All of the branches distal to these two points of fresh occlusion were well filled, however, with blue injection mass from the left coronary. This injection mass could have penetrated beyond the points of occlusion only through anastomotic channels. No other indications of an anastomotic circulation were disclosed in this heart.

Comment.—This case of severe, long-standing angina pectoris is in marked contrast to those without valvular disease described in Table I, in almost all of which there were old, complete occlusions of at least two main vessels and advanced coronary arteriosclerosis. This patient had only a small amount of scattered atherosclerosis, and no long-standing occlusions or areas of extreme narrowing. He differs from the others in one respect, namely, that he had long-standing mitral stenosis and insufficiency, and this valvular lesion may have been an important factor in the causation of the severe angina pectoris. White[3] states that "Hochrein[4] has found a narrowing of the mouth of the left coronary artery, pulled downward by the deformed anterior cusp of the mitral valve (in its turn held down by shortened chordae tendineae), in a case of mitral stenosis. This may explain the angina pectoris which occurs as a rare complication of mitral stenosis." Narrowing of the mouth, leading to stasis, would predispose to the formation of fresh thrombi. The fact that fresh thrombi were found in the terminal portion of the main stem and in one of the primary branches of the left anterior descending artery is in accord with this possibility. Stasis in the left anterior descending coronary artery probably predisposed to thrombosis, and infarction of the area supplied evidently resulted. The artery showed relatively little arteriosclerosis and was probably adequate until thrombosis occurred, but there was insufficient anastomotic circulation to prevent infarction. The heart had been laboring under the disadvantage of hypertension, mitral stenosis and

insufficiency, and, latterly, auricular flutter. It is of considerable interest that multiple thrombi were found under only one other condition in this series, i.e., in postoperative shock, when stasis was likewise presumably present. The long-standing angina pectoris is to be attributed to the greatly increased work and increased needs of the heart consequent to these conditions, rather than to arteriosclerotic obstruction of blood flow.

CASE 27.—Rheumatic heart disease; aortic insufficiency; cardiac hypertrophy; dyspnea and palpitation on exertion, ten years; edema of legs, two and one-half years; angina pectoris, five years; progressive congestive failure and death.

No coronary arteriosclerosis; no anastomotic circulation.



Case 27.—Diagram of coronary arterial tree.

History.—A. V., a 26-year-old student, was admitted to the hospital two and one-quarter years before death, complaining of palpitation, precordial pain, slight dyspnea, and hemoptysis. Beginning fourteen years prior to admission, he had suffered severe, recurrent attacks of rheumatic fever. Ten years before admission he noted dyspnea and palpitation on exertion. Three years prior to entry he began to experience occasional attacks of precordial pain, precipitated by heavy meals and occurring after exertion. During the four months before admission he also noticed occasional swelling of the ankles, slightly increased dyspnea on exertion, and, at times, coughed up bloodtinged sputum.

Physical examination showed moderate obesity, the characteristic peripheral signs of aortic insufficiency, a heaving precordium, and cardiac enlargement. The heart beat was regular; systolic and presystolic murmurs were heard at the apex, and systolic and diastolic murmurs at the aortic area characteristic of slight aortic stenosis and marked aortic insufficiency. The blood pressure was 200/20. There were râles at the base of the right lung; the spleen was palpable. A roentgenogram

showed that the transverse cardiac diameter was 22.5 cm., and the internal chest diameter, 31.6 cm.; the heart was markedly enlarged in the region of the left ventricle.

The electrocardiogram showed inversion of $T_{1, 2, 3}$, delayed A-V conduction, and right axis deviation. On a regimen of bed rest and digitalis his condition improved, and he was discharged on the ninth hospital day. Thereafter he noticed slight dyspnea on exertion, but was otherwise symptom-free for a time. One year before death, the dyspnea on exertion became progressively worse; this coincided with the development of auricular fibrillation. Digitalis and, later, quinidine were prescribed, and the rhythm became normal. One month before death, edema of the legs increased and the sputum was again bloodtinged. Despite complete rest in bed in the hospital, congestive failure grew progressively more marked; he became disoriented and confused, and died with general anasarca one month after admission.

Necropsy.—Heart: The heart weighed 1,380 grams. It was hypertrophied throughout, especially the left ventricle. Hydropericardium (900 c.c.) and some fibrous pericardial adhesions were present. There were no old or fresh infarcts and no gross or microscopic evidences of fibrosis. The aortic valve showed curling of the leaflets and definite insufficiency. There was some distortion of the mitral valve and its chordae tendineae, but it appeared to be functionally efficient. No Aschoff rheumatic nodules were found in the myocardium and there was no active rheumatic lesion in the valve sections. The other valves were normal.

Coronary Arteries: The coronary arteries showed no arteriosclerosis, no narrowings or occlusions, and no anastomoses. There was a very rich vascular tree commensurate with this unusually large heart.

Comment.—The predominant factors in this illness were active rheumatic infection and valvular insufficiency, resulting in progressive and fatal congestive failure. The attacks of precordial distress on exertion and after meals were clearly related to the increased needs of the hypertrophied myocardium and the relatively decreased coronary blood supply associated with the very low diastolic blood pressure of aortic insufficiency. This patient, who was observed by one of us, had had a continually active rheumatic infection prior to his terminal illness; inflammatory changes within the coronary arteries may have contributed to the production of the anginal pain.

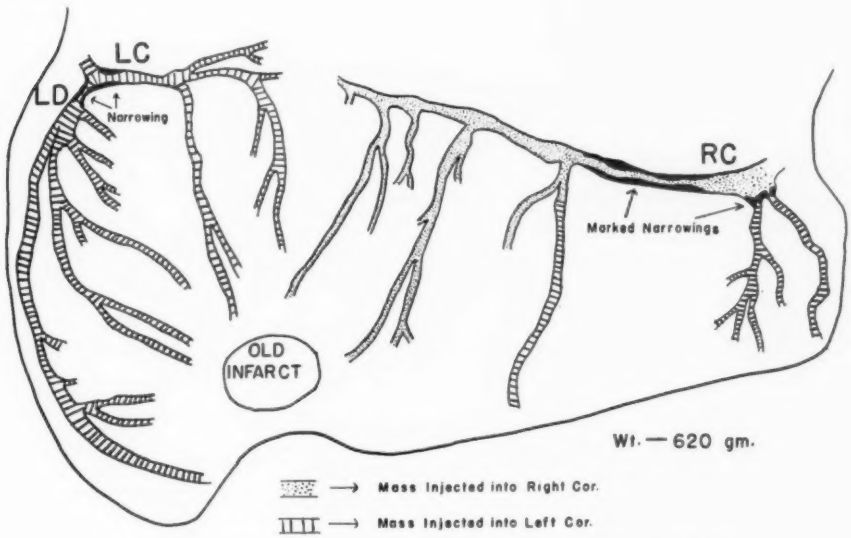
CASE 28.—Rheumatic heart disease, aortic and mitral stenosis and insufficiency; angina pectoris, six years; severe paroxysmal dyspnea, three years; phlebitis, and pulmonary infarction, causing death.

Myocardial fibrosis; old, small myocardial infarct; marked coronary arteriosclerosis, with narrowing but no occlusion.

History.—L. D., a 51-year-old steam-fitter, was admitted to the hospital one month before death because of severe pain in the chest, cough, and bloody sputum, of one day's duration. He had noted substernal pain which was precipitated by exertion for approximately six years, and for three years had had attacks of paroxysmal nocturnal dyspnea. A year before admission, while driving an automobile, he experienced an unusually severe attack of substernal pain which lasted twenty minutes; although he was forced to stop from time to time, he continued on his journey. Following this he felt very weak and remained in bed for two days. Paroxysms of nocturnal dyspnea became frequent, necessitating hypodermic injections nightly and complete rest in bed for three months. Thereafter the attacks of dyspnea disappeared, but he continued to have occasional attacks of substernal pain. Three

weeks before admission he developed pain in the left leg, with swelling of the calf and redness over a varicose vein. The day before admission he suddenly experienced severe pain in the right side of the chest anteriorly, which was aggravated by inspiration, and raised dark-red sputum.

Physical examination on admission showed dyspnea and orthopnea, and dullness and fine, crackling râles at the bases of both lungs. The heart was greatly enlarged, the rate rapid, the rhythm normal, and the sounds of good quality. The characteristic signs of aortic stenosis and insufficiency and of mitral stenosis and insufficiency were present. The liver was not felt. There was no edema. The blood pressure was 114/68. The electrocardiogram on admission showed left axis deviation, a P-R interval of 0.20 sec., and a QRS of 0.10 sec. T_1 and T_2 were erect; Q_4 was absent (right arm electrode over chest). Roentgenograms of the lungs showed a triangular area of density at the base of the right lung. The temperature on admission was 102.5° F., the respiratory rate, 36. The saphenous vein was ligated. Oxygen and digitalis were administered, and the temperature and pulse and respiratory rates became normal on the third day. His clinical course was asymptomatic and he made satisfactory progress until the morning of the thirty-first hospital day, when he suddenly complained of severe chest pain radiating to both arms. He became pulseless and cyanotic, and, although he responded temporarily to morphine, caffein, and heat, he died suddenly two hours later.



Case 28.—Diagram of coronary arterial tree and site of infarct.

Necropsy.—Lungs: Two fresh pulmonary infarcts were present.

Heart: The heart weighed 620 grams. There was a small area, measuring 2.5 by 3.0 cm., near the apex of the left ventricle, which was interpreted as being an old, healed infarct. In this area there were large patches of fibrous tissue replacing the muscle, and some thinning of the wall. Elsewhere, the myocardium showed only a slight degree of diffuse fibrosis. There were no fresh infarcts. The right auricular appendage contained an ante-mortem thrombus. The aortic valve showed marked calcification and fusion of the leaflets, with stenosis. The mitral ring was also calcified and the mitral leaflets distorted, with definite stenosis and insufficiency. The tricuspid and pulmonic valves were normal.

Coronary Arteries: There was a marked degree of arteriosclerosis, especially of the right coronary artery; the lumen was narrowed for a long stretch, and the

mouths of the branches were involved. In the left coronary artery the arteriosclerosis was confined to the proximal part of both branches. No points of complete occlusion, either old or fresh, were demonstrable in any of the arteries. However, some anastomotic circulation was evident between the left descending coronary artery and the branches of the right coronary artery in the region of marked arteriosclerosis. The vessel supplying the conus arteriosus anastomosed directly, by a small, but dissectible, vessel, with a branch from the left coronary, which is a rare occurrence.

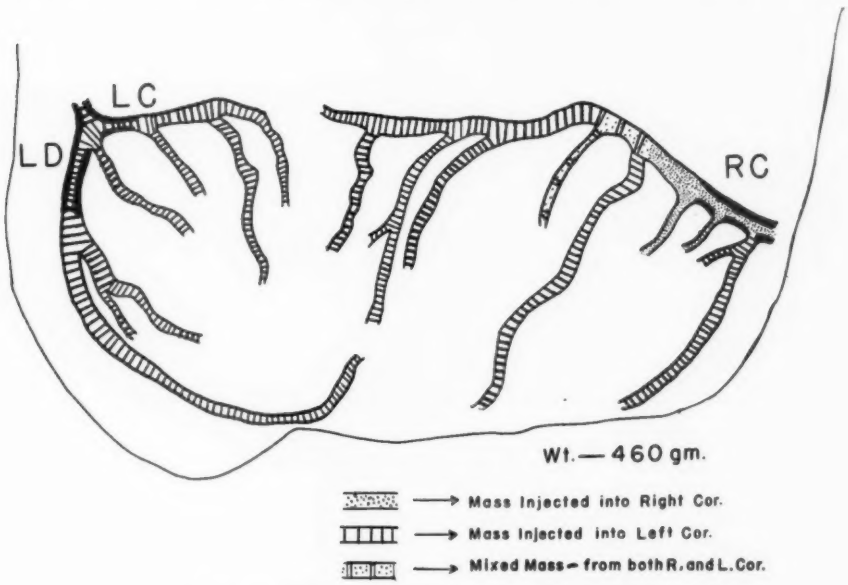
Comment.—This case again illustrates the occurrence of angina pectoris as a consequence mainly of valvular heart disease, rather than of coronary arteriosclerosis. There were no complete occlusions of any of the coronary arteries. While there was a rather marked degree of arteriosclerosis, especially of the right coronary artery, this had evidently developed slowly, and the anastomotic circulation was rich. In other cases in which there are no valvular lesions greater amounts of coronary selerosis are frequently observed without angina. In this patient the concomitant valvular disease caused considerably increased cardiac work and consequent hypertrophy. In brief, not only was there a need for greater blood supply because of increased work and hypertrophy, but also the coronary circulation itself was probably reduced. Focal myocardial necrosis resulted. Myocardial infarction in the absence of complete coronary occlusion may be caused by the coalescence of small areas of fibrosis or by sudden ischemia of a fairly large area in a zone supplied by a narrowed vessel. Under such circumstances, ischemia is not necessarily caused by further interference with blood supply, but may result from increased cardiac work and the increased demands made by exercise or emotion. If such an area receives an insufficient blood supply for a relatively short period, irreversible changes in the myocardial fibers may occur and necrosis may develop, even though a sufficient balance between supply of blood and myocardial requirements becomes established subsequently. The anastomotic vessels were particularly evident in the region of the heart supplied by branches distal to the areas of narrowing, and the area of infarction was in that portion of the heart furthest removed from the sources of blood supply. The severe attack of pain, one year before death, which recurred several times during the three subsequent hours when the patient continued to drive his automobile, was probably related to the development of this infarction. This case, like others in this series, exemplifies the tendency for ischemic areas to undergo necrosis rather than healing if the patient is not put at rest immediately after symptoms of severe cardiac anoxemia develop. It should be noted that this patient's heart showed an area of infarction without occlusion.

CASE 29.—Bronchial asthma, bronchiectasis, twelve years; cor pulmonale; congestive failure, two years; angina pectoris, six weeks; death caused by congestive failure and circulatory collapse.

Right ventricular hypertrophy; slight coronary arteriosclerosis.

History.—A man, S. B., 60 years of age, a rag-picker, was admitted to the hospital three days before death because of marked weakness of nine weeks' duration, increasing dyspnea and cough, peripheral edema, and attacks of precordial pain occurring with excitement and precipitated by exertion. He had had severe bronchial asthma for twelve years, as well as cough and hemoptysis, and had been treated for tuberculosis seven years before admission. During the two years previous to admission, he noted gradually increasing weakness, swelling of his feet, and dyspnea. For six weeks he had also noted pain in the anterior portion of the chest, which lasted five minutes to an hour, radiated to the right chest and left shoulder, was associated with severe dyspnea and palpitation, and was precipitated by excitement and exertion. The pain was never severe.

Physical examination on admission showed orthopnea, dyspnea, cyanosis, engorgement of the neck veins, moist, crackling, and sibilant râles over both lungs posteriorly, amphoric breathing and cavernous breath sounds in the right side of the chest below the scapula, and a regular, rapid heartbeat, with no murmurs; the liver dullness extended two fingerbreadths below the costal margin, but the edge could not be felt. Marked edema of both extremities, extending halfway up the shins, and pronounced clubbing of fingers and cyanosis of nail beds were noted.



Case 29.—Diagram of coronary arterial tree.

The electrocardiogram showed sinus rhythm and a rate of 100; T_1 was almost flat, T_2 was diphasic, T_3 was inverted, Q_4 was absent, and there was marked right axis deviation. On admission he was extremely dyspneic and coughed up large amounts of purulent sputum. He was placed in an oxygen tent for relief of cyanosis and dyspnea, was given caffein, morphine, and adrenalin, and was fully digitalized. The orthopnea and cyanosis increased, however, and he died in circulatory collapse on the third hospital day.

Necropsy.—Heart: The heart weighed 460 grams. Most of the hypertrophy was of the right ventricle, the wall of which was almost twice as thick as usual. Grossly, there were no infarcts, old or fresh. There was no diffuse fibrosis, grossly or microscopically. The valves were normal.

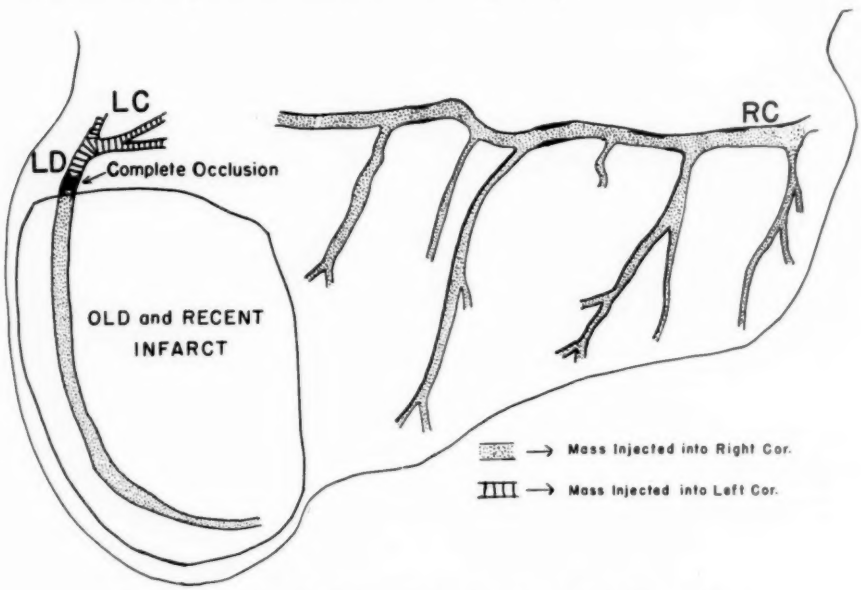
Coronary arteries: The coronary arteries showed only a few, scattered, atheromatous patches, most numerous near the beginning of all of the major vessels; there were no points of extreme narrowing or occlusion. However, there was a rich anastomotic circulation between the right and left coronary arteries; the right ventricle received blood from both coronary vessels.

Comment.—This patient, with severe bronchial asthma and bronchiectasis of twelve years' duration, developed congestive failure because of the increased strain on the right ventricle. The development of angina pectoris during the last few weeks was undoubtedly favored by the anoxemia and cardiac weakness, and, judging from our other findings, otherwise would probably not have occurred.

This case, in which there was no occlusion of any of the coronary arteries, shows that hypertrophy by itself in some instances may lead to the development of functionally significant anastomotic circulation, and that a blood supply sufficient for the needs of a normal heart may not be adequate in the presence of hypertrophy, particularly when coronary arteriosclerosis, increased work, or anoxemia is superimposed.

CASE 30.—Congestive failure, twenty-four months; attack of coronary thrombosis twenty-one months before death; angina pectoris, one year; cardiac asthma; death caused by a cerebral accident.

Large infarct, with aneurysm, of left ventricle; small left circumflex artery; old occlusion near origin of left anterior descending artery.



Case 30.—Diagram of coronary arterial tree and site of infarct.

History.—A man, A. L., a 54-year-old clerk, was first seen at the hospital approximately fourteen months before death, complaining of progressive weakness, dyspnea, palpitation, and edema. Ten months previously he noted the onset of weakness, dyspnea, and swelling of the ankles. Three months later, on walking

home, he suddenly experienced sharp pain in the chest, weakness, and sweating, and collapsed. Repeated injections of morphine were necessary for several days. He rested in bed for five weeks and for a few weeks thereafter was symptom-free. He then began to have attacks of paroxysmal nocturnal dyspnea, lasting 10 to 25 minutes, increasing in severity and frequency despite rest in bed. There was no severe precordial pain at any time after his first attack. Five months before admission orthopnea and dyspnea became progressively more marked.

Physical examination fourteen months before death showed orthopnea, cyanosis, marked retinal arteriosclerosis, râles over the lower half of the left side of the chest and at the base of the right lung, prolonged expiration, marked cardiac enlargement, a regular, rapid heartbeat, and distant heart sounds of poor quality; the edge of the liver was palpable at the costal margin, the dorsalis pedis pulsations were faint, and the feet were cold and pale. The blood pressure was 110/78. The vital capacity was 2.3 liters. A teleoroentgenogram showed a transverse cardiac diameter of 17.3 cm. and an internal chest diameter of 29.0 cm. Fluoroscopic examination showed marked enlargement of the heart, with aneurysm of the left ventricle. The electrocardiogram showed sinus rhythm, complete bundle branch block, a QRS interval of 0.16 sec., vibratory QRS complexes, low voltage of QRS and T in Lead I, absence of Q_1, and an upright T_1 (old method). He improved after the administration of diuretics and digitalis, but râles persisted at the bases of both lungs. He was discharged on the tenth hospital day and referred to a private physician for continuation of treatment.

Beginning twelve months before death, he began to experience severe, squeezing, epigastric pain which radiated to both sides of the chest. Attacks of paroxysmal dyspnea, sometimes preceded by, followed by, or unassociated with, pain in the chest also recurred as often as four or five times weekly. He was finally readmitted to the hospital, four months before death, because of these symptoms. Physical examination showed orthopnea, cyanosis, tremor of the head and extremities, moist râles at the bases of both lungs, and gallop rhythm; the edge of the liver was three fingerbreadths below the costal margin. While in the hospital he had several attacks of pain, associated with breathlessness. These were quickly relieved by nitroglycerin or morphine. He was discharged improved on the twentieth hospital day, but was admitted to the hospital a third time three weeks later, six weeks before death, because of severe left-sided chest pain which radiated around to the back and occasionally to the left flank. Physical examination again showed orthopnea, cyanosis, râles at the bases of both lungs, and gallop rhythm, but no peripheral edema. He remained in the hospital two weeks and appeared to be somewhat improved, although coarse râles were still heard at the bases of both lungs. He was then transferred to a hospital for chronic diseases, but soon after admission to this hospital he had frequent attacks of dyspnea with epigastric distress, and, after four weeks, developed a right-sided hemiplegia without losing consciousness. Two weeks later he became semicomatose and expired.

Necropsy.—Heart: The heart was not weighed. There was a large infarct occupying most of the anterior portion of the left ventricle and extending into, but not through, the anterior half of the septum. In a large area in this infarct the heart wall was only a few millimeters in thickness and was completely replaced by a fibrous tissue scar, which was bulging. Over this infarcted area within the ventricle there was a large ante-mortem thrombus which was mostly organized, but also contained some more recent thrombotic deposits. There was also an area of adherent pericarditis over this infarcted area. The rest of the myocardium showed only slight fibrosis. There were no other old or recent infarcts. The valves were normal.

Coronary Arteries: There were many scattered arteriosclerotic plaques in the right coronary artery, but none in the left circumflex coronary artery. The latter

vessel was small, and supplied only a small portion of the heart. The right coronary artery extended well over to the left ventricle. The left descending coronary artery showed a point of complete, old occlusion a short distance below its origin. This zone was not calcified. The vessel and its branches were almost completely bloodless and uninjected beyond that point. They were patent, however, and an anastomotic circulation from the right coronary artery into the infarcted area was just developing. This was coming up through the septal vessels; the right coronary alone was supplying the posterior part of the septum.

Comment.—This patient, with a small left circumflex artery and occlusion of the left anterior descending artery close to its origin, first showed signs of myocardial weakness twenty-four months before death, and, three months later, the clinical manifestations of myocardial infarction. At this latter time it is probable that the left anterior descending vessel became rapidly occluded, before a sufficient anastomotic circulation had developed. The size of the infarct attests to this inadequacy of the anastomotic circulation, for the present studies conclusively show that infarction is often absent in the presence of much more extensive occlusive disease when an adequate anastomotic circulation has previously developed. The congestive failure and the attacks of nocturnal dyspnea were undoubtedly caused by left ventricular weakness resulting from massive infarction and aneurysmal dilatation of its wall. The right coronary artery supplied much of the remaining noninfarcted portion of the left ventricle. The angina pectoris was evidently caused by arteriosclerotic involvement of this artery, with progressive narrowing of the lumen.

V. Discussion

A joint study from the clinical and pathologic points of view, such as the present investigation, affords insight into the mechanism of some of the symptoms and signs of coronary arterial disease and permits a fuller understanding of the progression of clinical events. While caution must be exercised when one infers changes in function from changes in structure, considerable advances in cardiac physiology and refinements in pathologic technique warrant certain interpretations hitherto not permissible. We are fortunate in having the histories and pathologic observations on some patients with clinical manifestations of coronary artery disease who died of intercurrent noncardiac disease. The cardiovascular status of such patients affords insight into the earlier stages of cardiovascular disease of other patients who finally succumb because of the end results of coronary arteriosclerosis.

1. Collateral circulation within the heart: its presence and significance

a. Cases in which there were no clinical evidences of cardiovascular disease and little or no coronary arteriosclerosis

Although Cohnheim and von Schulthess-Rechberg, in 1881,[5] believed, as a result of their studies, that the coronary arteries were end arteries,

it has gradually become the consensus that anastomotic circulation exists within the heart. Considerable literature is available on the subject and has been reviewed elsewhere.[6, 7] The functional significance of such an anastomotic circulation, the circumstances which may lead to its development, and its exact anatomic architecture are, however, still incompletely known. Competent authorities differ widely in their opinions. That an anastomotic circulation normally connects the capillaries and other finer vessels seems established. Gross,[6] Spalteholz,[7] and Campbell,[8] as a result of their studies, believed that, with increasing age, an anastomotic circulation also developed between precapillary vessels.

The results of the present investigation, as well as of those previously recorded,[1] are not, however, in entire accord with this view. In the hearts of even *senile* patients who had shown no clinical evidences of cardiovascular disease and had only minimal coronary arteriosclerosis or none at all, the injection of a lead-agar mass rarely revealed any evidence of an anastomotic connection between the left and right coronary arteries. The viscosity of the lead-agar mass is approximately three times that of blood, and it regularly penetrates to arterioles 40 micra in diameter. In practically none of the patients with no or minimal coronary arteriosclerosis, who died of noncardiac causes, was the red lead-agar mass which was introduced into the right coronary artery found in the branches of the left coronary arteries, nor was blue mass from the left coronary arteries found in the right coronary artery. Some of these patients were in the sixth, seventh, or eighth decades of life, when, according to Gross' observations with barium sulphate gelatine, anastomotic circulation might have been expected to be uniformly present. Since, under the conditions of injection at 45° C., barium gelatine has a viscosity of 18, as compared to 3 for lead-agar, relative to human heparinized blood at 37° C., the difference in results cannot be ascribed wholly to difference in materials used for injection. In the hearts which we studied, when no significant coronary arteriosclerosis was present, intercoronary communicating vessels were too small to be demonstrated by the technique used, regardless of the age of the subject. It appears, therefore, that, irrespective of the age of the individual, anastomoses measuring 40 micra, or more, in diameter, between the right and left coronary arteries, usually do not exist in the absence of partial or complete occlusions of these arteries.

When, however, in such normal hearts, red-colored *watery* solutions were injected into the right coronary artery, some of the injected material could be visualized regularly in the branches of the left coronary artery. Conversely, when blue-colored *watery* solutions were injected into the left coronary artery, some of the injected solution was always found in the branches of the right coronary artery. Simul-

taneous injection of such solutions into the mouths of the right and left coronary arteries resulted in fusion of the colors and the production of purplish areas. It cannot, of course, be stated on the basis of these observations whether these connections are chiefly between capillary or precapillary vessels. Since in the same hearts a subsequent unilateral injection of lead-agar did not reveal such anastomoses, it can be concluded that the diameters of the connecting vessels in normal hearts are less than 40 micra.

It would seem evident from these observations that fine communications regularly exist between the right and left coronary arteries in hearts showing no evidence of disease. These finer communications are, however, of but questionable functional significance. As Wiggers[9] has stated:

"From a pathological standpoint it has long been accepted that the coronaries are terminal arteries, for when plugged by emboli or thrombi in man or when artificially occluded in animals, an infarct results. The rapid necrosis of cardiac tissue could scarcely occur, were adequate anastomoses present."

He further quotes W. T. Porter,[10] who stated that:

"The objection that one of the coronary arteries can be injected from another, and that therefore they are not terminal, is based on the incorrect premise that terminal arteries cannot be thus injected, and has no weight against the positive evidence of the complete failure of nutrition following closure. The passage of fine injection-mass from one vascular area to another proves nothing concerning the possibility of the one area receiving its blood supply from the other. Such supply is impossible if the resistance in the communicating vessels is greater than the blood pressure in the smallest branches of the artery through which the supply must come. It is the fact of this high resistance, due to the small size of the communicating branches, which makes the artery 'terminal.' This condition of high resistance is really present during life, or infarction could not take place."

In summary, then, it may be stated that, regardless of the age of the subject, normal hearts in which there is little or no coronary arteriosclerosis regularly have fine intercoronary communications, but do not possess an anastomotic circulation through vessels large enough to be functionally significant in obviating the untoward results of rapidly developing coronary narrowing or occlusions.

b. The importance of the development of a collateral circulation when the coronary arteries are narrowed or occluded

In contrast to the above-noted absence of demonstrable, functionally significant anastomoses in normal hearts are the findings in hearts in which there are old, long-standing, complete occlusions, or extreme narrowing, of the main coronary arteries and their branches, from patients who had had no significant symptoms of heart disease. In

thirteen cases (Table II) in which there were advanced coronary arteriosclerotic changes and consequent obstruction to normal blood flow, the patients had not suffered from angina pectoris. Nine of these thirteen patients also had had no symptoms or signs of congestive failure. In accord with these clinical data was the general absence of diffuse pathologic changes in the myocardium. In only five of the thirteen hearts in this group was there myocardial fibrosis, and, of these five, four presented this change to a slight degree, and one to a moderate degree. In only two of the thirteen hearts was there an area of old infarction.

This seeming inconsistency, namely, the presence of long-standing obstructive arterial lesions and the absence of significant pathologic or clinical evidence of myocardial damage, is dispelled by the demonstration that a collateral circulation exists. Despite extreme vascular narrowing, or even multiple, old occlusions of the coronary arteries, the neighboring myocardium was richly provided with vessels which were well filled by the lead-agar mass injected into the mouths of the right and left coronary arteries. The injection of a red-tinted mass into the right coronary artery and of a blue-tinted mass into the left coronary artery revealed significant information regarding the source of the vascular filling which was always found in the areas distal to the zones of old occlusion. In some instances the main artery and its branches distal to the occluded portion were injected via anastomotic vessels arising from the same artery or its branches proximal to the occlusion. In this event the vessels proximal and distal to the occlusion contained injection mass of the same color. In other hearts, the proximal portion of an occluded left anterior descending artery, for example, was filled with blue mass, while the terminal portion was filled with red mass, clearly indicating that the anastomotic circulation was derived from the opposite, right coronary artery. When the right coronary artery was completely occluded, the terminal portion was frequently filled by blue injection mass from the left coronary arteries. Some vessels beyond the occluded or narrowed zones were not infrequently filled with purple injection mass, indicating that the anastomotic circulation was derived in part from the right and in part from the left arteries.

It appears that in human hearts anastomotic circulation develops only *when* and *where* it is needed. In Case 14, in which death was caused by carcinoma of the stomach and gastrointestinal hemorrhage, there were no occlusions in the three major arteries, but one of the largest branches of the left circumflex artery was completely occluded and calcified for a distance of approximately three centimeters from its origin. The distal portion of the occluded artery was well injected through anastomotic vessels from neighboring branches of the left coronary artery; there was no anastomotic circulation elsewhere in this heart. That the anastomotic circulation develops only in regions

where it is needed is also shown in Case 28. Although there were no complete arterial occlusions, an anastomotic circulation had developed about the sites of extreme arteriosclerotic narrowing, and there only.

Throughout these studies, evidence of an anastomotic circulation was almost invariably disclosed in relation to considerable narrowing or old, complete occlusions of the coronary arteries or their main branches. These evidences of anastomotic circulation were never found in the normal hearts of this series, nor in those parts of diseased hearts in which the circulation was normal, except under certain unusual circumstances of increased requirements to be described later.

The anatomic studies, to date, do not afford an explanation of the various factors involved in the establishment of this anastomotic circulation. It would seem, however, that, consequent to progressive narrowing and final occlusion of a particular vessel, the pressure in the arterial segment beyond the affected zone must become progressively reduced. This would favor an increase in the size of channels which communicate with other relatively uninvolved arteries containing blood under higher pressure. In the absence of previous narrowing or occlusion, these communicating channels are too small to be injected by the somewhat viscid agar mass utilized in these studies. Other possibilities should be mentioned: Clark and his associates[11] have suggested that biotactic reactions may lead to the development of new vessels, while Winternitz and his associates[12] indicate that the vasa vasorum may help to form a collateral circulation. These questions, as well as a study of other types of collateral circulation which may be disclosed by techniques differing from those here employed, require further investigation.

Arteriosclerosis of the coronary arteries, as in other locations, is usually irregular in distribution and causes narrowing of the various arterial lumina to different degrees. The complexity and variations in the distribution of the component vessels of the anastomotic circulation are therefore almost unlimited. Moreover, if the patent portions of vessels serving as sources of the anastomotic circulation become involved later, further variations in the anastomotic patterns may be superinduced.

That this anastomotic circulation may compensate for coronary artery occlusions to a degree sufficient to enable the heart to meet the demands of the ordinary activities of life is amply demonstrated by the cases in Table II.

The many gradations of narrowing seen in the vessels of these hearts indicate that encroachment upon the lumen frequently takes place slowly. When narrowing, progressing even as far as occlusion, proceeds gradually, first in one part of the coronary tree and then in another, complete occlusion of two or even of all three main coronary arteries may be compatible with continued life. Most patients exhibiting this condition, particularly when the third, unoccluded, artery

is greatly narrowed, experience angina pectoris or congestive failure. Occasionally, these clinical manifestations and gross evidence of myocardial fibrosis post mortem may be absent (Cases 16, 17). The injection of such hearts demonstrates an extraordinarily rich network of anastomotic vessels; all semblance of end arteries is lost.

It should be pointed out, however, that although a compensatory anastomotic circulation which has developed during the gradual occlusion of a coronary artery might be sufficient to supply the usual needs of the heart, the margin of safety, or, as it may be termed, the "coronary reserve," would be clearly reduced. Those of our patients with multiple coronary occlusions generally had angina pectoris or congestive failure during life and myocardial fibrosis post mortem. This is hardly surprising, for the fact that the flow of blood through these anastomotic channels must necessarily be circuitous would inevitably lead to a reduction in the gradient of pressure and marked slowing of the circulation. In many instances, moreover, the direction of blood flow in the segments of vessels beyond the zones of narrowing or occlusion is unquestionably the reverse of normal.

The rate at which collateral circulation can develop would seem, from these studies, to be slow. In instances in which the occlusion of a relatively uninvolved vessel occurred suddenly, because of thrombosis, the physiologic and anatomic consequences were similar to those produced experimentally in animals when an artery is ligated suddenly (Cases 21, 23, 25). Persistent, severe pain and, frequently, collapse are observed clinically, and massive infarction post mortem. Many intermediate stages exist between this extreme and the other, in which narrowing proceeds so very slowly that the adequately developed collateral circulation prevents any clinical or pathologic manifestations when final occlusion occurs.

In general, it seems that when occlusion progresses more rapidly than the collateral circulation develops, myocardial anoxemia and necrosis are prone to occur. This is most vividly portrayed by Cases 21, 22, and 24. In these hearts there were fewer coronary artery occlusions than in many in Table I and Table II, section a, but the rapid formation of a coronary thrombus before an adequate collateral circulation had been established led to sudden death. In the hearts in Cases 19 and 20, in which there were old, healed infarcts, a considerable collateral circulation may well have been established before the final occlusion of the main arteries took place, thus permitting continuation of life with healing of the infarcted area.

c. The significance of collateral circulation in the absence of coronary arterial narrowing or occlusion

Besides the above-mentioned most common cause for the development of a collateral circulation, myocardial hypertrophy with its

increased nutritional requirements should also be discussed. In the presence of rheumatic valvular disease or arterial hypertension, an anastomotic circulation has been found with little or no coronary arterial narrowing or occlusion. Gross,[6] in his studies, demonstrated that the capacity of the arterial tree is increased in cardiac hypertrophy, while Russow[13] and Fishberg[14] found that the total cross section of the primary coronary branches is enlarged in such hypertrophied hearts. The occurrence of an anastomotic circulation in the presence of hypertrophy may signify a dilatation of the finer communications which are normally present, similar to that found in the larger vessels by the above-mentioned authors. An anastomotic circulation with little or no interference with coronary blood flow was found in Cases 26 and 29, in which the primary factors causing cardiac hypertrophy were arterial hypertension, cor pulmonale, and rheumatic heart disease. To summarize, increased work of a part of the myocardium and, consequently, increased local cardiac needs may stimulate the development of an anastomotic circulation even if the coronary arteries themselves are quite normal. The proportion in which these two factors of hypertrophy and coronary obstruction operate in a given heart probably varies from case to case. If the anastomotic circulation is insufficient, local anoxia and pain may result.

2. THE PATHOLOGIC BASIS FOR ANGINA PECTORIS

The purpose of this study of the pathologic basis for angina pectoris is to gain insight into the condition of the heart in patients with angina pectoris as we encounter them clinically. In the correlation of the cardiac changes with the signs and symptoms of angina pectoris, the events of the terminal illness and the presence of fresh cardiac lesions disclosed post mortem need not be considered.

When the patients with complete, old coronary artery occlusion are grouped according to whether they had had angina pectoris (Table I) or no angina pectoris (Table II), certain definite and interesting differences are disclosed. Of the twelve cases in which angina pectoris had been the primary cardiac disease, in ten there were zones of old, complete occlusion in at least two of the three main coronary arteries, and these occlusions clearly antedated the terminal illness; in three (Cases 1, 2, and 3) of these ten hearts, all three main arteries had been occluded. In the seven cases in which two major coronary arteries were occluded, the third main coronary artery was almost occluded in five (Cases 5, 6, 7, 9, and 10), and in three (Cases 4, 5, and 6), occlusions in primary branches as well as in the main arteries were found. Six fresh occlusions, which occurred in five cases, were responsible for death. They are not included in the above analyses, for angina pectoris, according to the histories, had been present prior to the occurrence of these terminal occlusions.

Of this group of twelve cases of angina pectoris, in the two exceptional cases (Cases 11 and 12) in which there was only one point of old, complete occlusion in the right coronary artery prior to the final illness, there was, besides this complete occlusion, decided diffuse arteriosclerotic narrowing of the other two arteries, which must have reduced the blood flow considerably. The multiple, widespread narrowing of the unoccluded arteries would tend to interfere with the full development of an adequate anastomotic blood supply to compensate for the occlusion of the right coronary artery. Objective confirmation of these considerations is afforded by the diffuse myocardial fibrosis found in both hearts. In both cases the widespread myocardial involvement had led to congestive failure. It should be noted that no patient with angina pectoris failed to show a zone of old, complete occlusion in at least one of the major coronary arteries, with the exception of those with rheumatic heart disease or cor pulmonale (Table III).

The foregoing observations in a group of patients with angina pectoris are to be contrasted with those in the thirteen hearts in which there was occlusion of at least one coronary artery or a primary branch, taken from patients who had never manifested the symptoms of angina pectoris (Table II). In two (Cases 21 and 22) of these thirteen hearts there was one narrowed main artery in which a thrombus had been freshly deposited. In two other hearts (Cases 14 and 24) there was old, complete occlusion of only a primary branch, but with additional narrowing of a main coronary artery in one (Case 24). In six (Cases 13, 15, 18, 19, 23, and 25) of these thirteen hearts there was complete, old occlusion of only one main artery. In only three of these thirteen hearts (Cases 16, 17, and 20) were there complete occlusions of two main arteries which clearly had been present for some time.

The occurrence of twenty-five completely occluded major arteries, of which, in the twelve hearts from patients with angina pectoris (Table I), the occlusions clearly antedated the final illness, is in contrast to that of but twelve such completely occluded major coronary arteries in the thirteen hearts (Table II) from patients who did not have angina pectoris but nevertheless showed unequivocal coronary artery disease. There is, however, some overlapping in the two groups. It must therefore be concluded that gross changes in the coronary circulation are not the sole determining factor with respect to the presence or absence of angina pectoris. This is further exemplified by the five patients with angina pectoris, included in Table III, who had valvular disease or in whom the congestive failure preceded or accompanied the angina pectoris, for the hearts of these patients showed relatively little coronary arteriosclerosis. The absence of decided interference with the coronary blood flow in the hearts of these patients would lead

one to suspect, according to the foregoing discussion, that angina pectoris and congestive failure in these subjects were caused predominantly by greatly increased work of the heart. An examination of the data shows that this is indeed the case. Considerable or extreme degrees of hypertrophy were present in all of these hearts. Three of the five hearts were the seat of advanced rheumatic valvular disease; in two of these patients the blood pressure had been greatly elevated. In one patient with cor pulmonale secondary to severe bronchial asthma and bronchiectasis, the occurrence of angina pectoris during the last six weeks of life was undoubtedly favored by the additional anoxemia caused by pulmonary disease, and by the presence of active pulmonary infection.

There remains for consideration the rather unusual case (Case 30) in which, although but one coronary artery was completely occluded and no arterial hypertension existed, the patient nevertheless suffered from congestive failure for two years and angina pectoris for one year. The disability of this patient over a period of two years was related to the occurrence of sudden occlusion of the left anterior descending artery, which produced the clinical manifestations of cardiac collapse because of an extraordinarily massive infarction involving most of the anterior portion of the left ventricle and the anterior half of the interventricular septum. The abrupt appearance and continued manifestations of congestive failure following this extensive loss of myocardial tissue are readily understandable, as are the attacks of angina pectoris.

The anatomic findings in every case of angina pectoris in this series are consistent with the theory that angina pectoris is the result of paroxysmal, relative, myocardial ischemia. In each patient with angina pectoris listed in Table I, the maximal blood supply originally available to the myocardium had been obviously reduced by arterial occlusions or narrowing. Under such conditions, anything which further reduces the available blood supply or increases the nutritional requirements (oxygen, etc.) of the heart, or circumstances which increase the work of the heart beyond that which can be sustained by the reduced blood supply, lead to ischemia or anoxemia and pain. This theory, propounded by Parry,[15] Jenner,[16] Burns,[17] and Keefer and Resnik,[18] has received substantial support by several recent investigations. Rothschild and Kissin[19] observed that attacks of angina pectoris could be induced by inhalation of air containing low oxygen percentages, and Riseman and Brown[20] were able to prevent attacks by having subjects with angina pectoris breathe pure oxygen during exercise. The anatomic studies reported in this communication provide an adequate structural basis for the operation of these physiologic factors. That such local anoxia, if severe enough and prolonged enough, can lead to necrosis of some of the involved muscle fibers is indicated

by the much greater incidence of patchy fibrosis in the hearts in the cases in Table I than in those in Table II.

The "coronary reserve" is thus considered as being reduced by those factors which decrease the supply of blood, or by those factors which increase the myocardial demands. Foremost among the factors which decrease the supply is mechanical obstruction to blood flow. Coronary arteriosclerosis is the most frequent cause. In syphilitic and rheumatic heart disease, obstruction of the mouths of the coronary arteries or inflammatory changes in the lumina may be present. However, pulmonary infection or edema, leading to anoxemia, and the fall in blood pressure in shock and perhaps during sleep are other factors frequently of great importance in decreasing the supply of nutritional elements to the heart. Among the factors which increase the work of the heart, and, therefore, its metabolic demands, are exercise, arterial hypertension, emotion, valvular obstruction or insufficiency, anemia, a rapid ventricular rate, thyrotoxicosis, and infection. The increased myocardial bulk caused by cardiac hypertrophy also increases the demand, which, as Wearn and his collaborators[21, 22] have shown, is often not adequately met by a corresponding increase in vascularization.

The theory that arterial spasm may produce paroxysmal, relative, myocardial ischemia is as yet unproved. The difficulty of visualizing spasm of the rigid, arteriosclerotic arteries in patients with angina pectoris is frequently pointed out. It is possible, however, that the inability of such vessels to dilate during exercise may be a significant factor contributing to the inadequate blood supply. Since the collateral network usually includes segments of vessels with relatively little arteriosclerosis, the possibility of vasoconstriction and vasodilatation cannot be entirely disregarded. It is conceivable that these nonrigid anastomotic vessels may respond to the effects of nitroglycerin.

Anginal pain in four of the five patients listed in Table III was precipitated not so much by decreased blood flow caused by coronary arteriosclerosis, as by increased work of the heart as a whole, consequent upon inadequately functioning valves (Cases 26, 27 and 28) or pulmonary obstruction (Case 29). In these cases the following contributing factors were also operative: increased cardiac work secondary to arterial hypertension; the decreased diastolic pressure of aortic insufficiency, tending to diminish the coronary circulation; the anoxia of congestive failure; and, finally, the effect of hypertrophy itself. As has been pointed out by others,[23, 24, 22] the increased bulk of the hypertrophied heart requires a greater than normal flow. Although the coronary flow is probably increased in such hypertrophied hearts, this increase may not keep pace with the increase in requirements caused by the above-mentioned factors.[25] This burden which

fell on the entire ventricle may have been responsible for the early onset of congestive failure in these cases. That the "coronary reserve" can be reduced by increased needs of the myocardium as well as by occluded arteries is also indicated by the striking tendency of hypertrophied hearts to develop an anastomotic circulation even if only slight narrowing of the coronary circulation is present. In Case 29 a considerable anastomotic circulation had developed with only slight narrowing of the major coronary arteries, suggesting that the normal circulation may be inadequate for the hypertrophied myocardium under such circumstances.

The occurrence of anginal pain in patients with valvular disease but with little or no arteriosclerotic coronary narrowing may also be favored by obstruction of the mouths of the arteries, as in syphilitic aortitis, or, as has been pointed out by Hochrein,[4] by rheumatic distortion of the coronary orifices. The reduced mean arterial blood pressure in aortic regurgitation and active rheumatic inflammatory changes in the blood vessels may also be significant factors.

3. THE PATHOLOGIC BASIS FOR CONGESTIVE FAILURE IN PATIENTS WITH CORONARY ARTERIAL DISEASE OR ANGINA PECTORIS

As has been previously stated, the observations in every case of angina pectoris in this series are consistent with the theory that angina pectoris is the result of paroxysmal, localized, relative, myocardial anoxemia. The precipitation of angina pectoris by factors which increase the work of the heart, such as emotion and exercise, and the relief of pain when the work of the heart is diminished, as it is at rest, lend credence to this theory.

We have found in previous experimental work[26, 27] that brief, temporary interference with blood flow in one artery may be followed by no permanent structural damage to the heart muscle if the normal blood supply is re-established after five to twenty minutes by releasing the constricting ligature. If interference with blood supply is continued for more than twenty minutes, localized areas of necrosis and fibrosis, or even massive infarction, are produced. The experimental results on the normal heart of the anesthetized dog cannot be applied in all details to the diseased heart of man; the general pathologic physiologic concept underlying both conditions is, however, the same.

The duration of attacks of angina pectoris is generally less than the period of twenty or more minutes of local ischemia which is necessary to produce focal necrosis and secondary fibrosis in normal dogs' hearts. It is readily understandable, however, that constantly undernourished areas in the human heart which is the seat of coronary arteriosclerosis could withstand a further increase of anoxemia caused by exertion or emotion with even less success than does the normal dog heart. Thus, it is probable that anginal attacks not infrequently

leave their mark on the myocardium in the form of fibrous scars. This progressive replacement of myocardial fibers by connective tissue should lead inevitably to myocardial weakness and congestive failure.

In general accord with the above considerations are the clinical observations recorded earlier in this communication, particularly the frequency with which foci of fibrosis were found in the hearts of patients with angina pectoris who had no valvular disease (Table I). Those hearts with the greatest degree of replacement of myocardial fibers by areas of fibrosis were found without exception in patients who, after months or years of angina pectoris, finally suffered from congestive failure (Cases 1, 2, 9, 10, 11, and 12).

Considering the group as a whole, of the thirty cases included in Tables I, II, III, there were fifteen in which there had been clinical evidence of congestive failure varying from one month to eleven years in duration. Thirteen of the fifteen patients without congestive failure were found to have no, or very slight, fibrosis of the myocardium, and none of them had marked fibrosis. On the other hand, six of the fifteen patients with congestive failure had moderate to marked fibrosis of the myocardium, and only four of this group showed no increase of fibrous tissue. In three of the four (Cases 13, 26, and 29), rheumatic valvular heart disease was present.

The above correlations between myocardial fibrosis and congestive failure are not absolute, nor, indeed, are perfect correlations to be expected. Estimations of the degree of myocardial fibrosis in this series were, at best, approximate; we are at present elaborating more exact methods for making such estimations. Moreover, the gradual sequence of events described above was suddenly interrupted in some patients by the occurrence of myocardial infarction, which, immediately depriving the heart of an important part of its musculature, led to the abrupt appearance of congestive failure. Many other variable factors, such as arterial hypertension, effort, infection, and tachycardia, likewise are important in the etiology of congestive failure.[28] Furthermore, it should be noted here that attacks of angina pectoris on only slight or moderate exertion prevent the individual from undertaking degrees of exertion which would tend to make the whole heart fail, and give rise to congestive failure. Conversely, generalized myocardial weakness, appearing early and leading to dyspnea on slight effort, tends to restrict the patient's activities and therefore lessens the incidence of attacks of angina pectoris.

4. THE PATHOLOGIC BASIS FOR THE SYNDROME OF "CORONARY OCCLUSION"; I.E., PROLONGED CORONARY FAILURE WITH MYOCARDIAL ANOXIA

The present studies indicate that there is no characteristic syndrome necessarily associated with coronary arterial occlusion per se. Thrombosis of a major coronary artery may occur without the syndrome of

"coronary occlusion" and, contrariwise, the syndrome may occur without a concomitant fresh thrombosis (Cases 3, 19, and 28). The clinical manifestations frequently designated by the terms "coronary thrombosis" or "coronary occlusion" are in fact caused by acute myocardial ischemia. Our observations are in accord with the current belief that both angina pectoris and so-called "coronary occlusion" are clinical manifestations of myocardial ischemia. In both of these syndromes the underlying mechanism seems to be a relative disproportion between the demands of the heart for blood and the supply of blood through the coronary arteries; the changes in the myocardium resulting from this disproportion depend solely upon the extent and duration of the relative ischemia, not on the manner in which it is produced.

In patients dying with the syndrome of "coronary occlusion," i.e., prolonged, crushing chest pain with the signs and symptoms of collapse, the frequent disclosure of a fresh, occluding thrombus or embolus has led to the assumption that thrombosis or embolism of a coronary artery always precipitates these symptoms and signs and that they are produced in no other way. Our observations demonstrate that such is not the case; thrombosis of a coronary artery produces symptoms only if myocardial ischemia follows. When the previous narrowing has been gradual, with concomitant development of an adequate collateral circulation, the final occlusion of the vessel may be asymptomatic, and myocardial necrosis may be entirely absent. Our repeated finding of long-standing complete occlusions, with no history of symptoms and no severe myocardial damage post mortem, is unequivocal (Table II). Also, in other cases (Cases 1, 2, and 3), long-standing occlusion of all three major arteries may be present, and the patients have angina pectoris but no areas of old cardiac infarction. When, however, the complete occlusion of a particular vessel is sudden, and other sources of supply are inadequate, ischemia regularly occurs, with accompanying clinical manifestations of pain, and if the ischemic area is sufficiently large, and ischemia sufficiently prolonged, cardiac weakness, collapse, and death may follow.

The production of myocardial ischemia in patients with coronary disease does not inevitably result in myocardial necrosis. If after such an accident the demands on the myocardium are quickly reduced by rest in bed, sedatives, or the control of rapid ventricular rates, sufficient collateral blood flow may be available to satisfy the lowered cardiac requirements and permit recovery of the anoxemic fibers. The electrocardiographic changes then disappear, and no clinical evidences of myocardial necrosis, such as fever, leucocytosis, or increased sedimentation rate, develop.

Our experiences in relating the electrocardiographic changes to the clinical and pathologic data in these cases accord in general with the

observations of others.[29, 3, 30, 31] Further discussion of this correlation will be reserved until more extensive observations are available.

Several patients in this series showed many of the striking characteristics of "coronary occlusion," but at post-mortem examination were found to have no infarction which could be related to such an attack (Cases 6 and 7). One of these patients (Case 6) is of particular interest because he had been admitted to a hospital immediately after the onset of excruciating, persistent, crushing, substernal pain. He was ashen, the blood pressure was 80/60, the pulse rate was 140, the pulse was thready, and signs of pulmonary edema were present. A cardiologist at that time stated that "The recent, acute, pulmonary edema, electrocardiographic changes, and poor quality of the first heart sound make me believe that he had a coronary thrombosis." The leucocyte count on admission and repeatedly during his stay was, however, normal. After rest in bed for six weeks and the administration of sedatives, he was discharged from the hospital. Post-mortem examination of the heart of this patient, three and a half years later, revealed, however, no old infarct. Similarly, in Case 7 the patient suffered several attacks of severe substernal pain lasting one-half hour, with a fall in blood pressure and weakness, necessitating rest in bed in the hospital for several weeks. The temperature and leucocyte count were normal. No infarcts were disclosed post mortem. Thus, myocardial anoxemia sufficiently severe to induce even prolonged pain may not necessarily lead to necrosis if rest in bed and sedatives are utilized. In such cases the symptoms and physical signs strongly suggest myocardial infarction, but the other confirmatory signs, such as fever, leucocytosis, an elevated sedimentation rate, and characteristic electrocardiographic changes, are lacking.

This sequence of events is analogous to that found in experimental studies[27, 32] in which a single, main coronary artery was isolated and temporarily occluded at one point by pressure. Deprived of its normal blood supply, the involved myocardium failed to contract within one minute of the onset of occlusion. If the period of deprivation was twenty minutes, or less, and a normal blood supply was then restored by releasing the ligature on the coronary artery, the heart regained its contractile ability immediately, and showed no pathologic changes. Longer periods of ischemia resulted in actual necrosis of the muscle, with replacement fibrosis.[27]

It is clear, therefore, that no accurate prediction can be made as to the pathologic changes in the heart in patients with the syndrome of "coronary occlusion." Infarcts may or may not be present, and, indeed, fresh thrombi may also be absent. If the relative disproportion between the demands of the heart for blood and the supply of blood through the coronary arteries is of brief duration, the duration

of pain is correspondingly brief, and angina pectoris is present. If the duration and degree of the disproportion between the supply of blood and the demands of the heart are sufficiently great, myocardial infarction develops. Between these two extremes intermediate conditions exist. The pain may persist longer than it usually does in angina pectoris, but evidences of structural myocardial damage, such as an increased sedimentation rate,[33] leucocytosis, and characteristic electrocardiographic changes, do not occur. This condition of prolonged myocardial anoxia may be designated "coronary failure."

5. THE PATHOLOGIC BASIS FOR THE PRODUCTION OF MYOCARDIAL INFARCTS AND COALESCENT AREAS OF MYOCARDIAL FIBROSIS

The above considerations lead to the conclusion that myocardial infarction is produced under circumstances which result in prolonged myocardial anoxia. Myocardial necrosis may occur (1) following sudden occlusion of a previously adequate arterial lumen *before* a fully adequate anastomotic circulation has had an opportunity to develop; or (2) without fresh occlusion of any of the main coronary vessels or their larger branches under circumstances, such as increased cardiac work, which predispose to prolonged myocardial anoxia.

The first mechanism was found operative particularly in Cases 21, 22, 23, and 25. Case 26 most nearly exemplifies the traditional concept of an infarct resulting from a coronary occlusion in an almost normal coronary tree. In some cases (Cases 21 and 23) there were fresh infarctions; within such areas an anastomotic circulation must have been present for a considerable period of time before the sudden occlusion occurred. In these cases, acute occlusion of a large vessel evidently occurred before an anastomotic circulation sufficient to sustain the myocardium when the blood supply was suddenly markedly reduced had developed. Such sudden narrowing obviously proceeded more rapidly than the development of anastomotic circulation.

The second mechanism presumably was operative in those cases in which myocardial infarction was found in the absence of any coronary thrombosis (Cases 3 and 28). Several possibilities must be considered. It is, of course, conceivable that fresh thrombi were overlooked or dislodged. We do not believe that this explanation is plausible, especially since meticulous care was naturally exercised in the search for thrombi and occlusions in such cases. Also, the fact that many freshly thrombosed vessels were found in other hearts in which there were no fresh infarcts (Cases 4, 7, 8, 11, 12, 22, and 24) attests to the accuracy of this method for detecting such thrombi.

It is more nearly in accord with our other observations to consider that in a heart with multiple occlusions and narrowings, and thus with an anastomotic, but reduced, blood supply, slight further nar-

rowing of several blood vessels, or increased demands on the myocardium because of rapid ventricular rates, could produce a large area of ischemia. This ischemic area then may undergo necrosis, with the production of a large infarct. In several of the cases (Cases 4, 21, 22, and 23), the production of infarction was undoubtedly favored by the fact that these patients did not rest after the onset of occlusion, but continued to work or persist in other activity, thereby prolonging ischemia. Another case (Case 28) is of interest in this respect. This patient, who one year before death experienced pain soon after the onset of a journey, nevertheless drove his car to his destination, a distance of 260 miles, despite persistent, intense pain. His heart showed a large, healed infarct, but even one year after the above episode there was no completely occluded vessel. This patient showed the least coronary involvement of any of those who died with myocardial infarction.

Some hearts (Cases 4, 9, 10, 11, 19, and 20) showed areas of fibrosis which were larger than the diffusely distributed, small foci commonly seen in the fibrous myocarditis associated with angina pectoris. These areas would ordinarily be regarded as healed infarcts. However, these patients presented nothing in their histories to suggest "acute coronary thrombosis." Such areas were often more irregular in outline, and the fibrosis within them more patchy in distribution, than might be expected in a definite myocardial infarct caused by sudden coronary thrombosis. Therefore, they may represent a coalescence of small areas of fibrosis following repeated focal myocardial ischemia. The fact that such "infarcted areas" were found predominantly in the hearts from patients with angina pectoris is in accord with these considerations. In most instances, the vessels leading to, and within, such areas of marked fibrosis were well injected.

On the other hand, some of the large, incompletely fibrosed myocardial areas may have been the end result of much more widespread ischemia, but many of the muscle fibers did not become necrotic because the patient was confined to bed, or the work of the heart was otherwise diminished. The prior development of some collateral circulation would nullify the effect of a sudden occlusion in these cases. Whatever collateral circulation had developed would naturally favor the survival of part of the musculature. It is pertinent in this connection to recall that the ligation of coronary arteries in normal dogs results in infarcts which are smaller than the area which shows the immediate effects of such an interruption of its blood supply.[34] The normal anastomotic pattern in the dog's heart will be the subject of a further study.

On the basis of the considerations in this and the preceding section, an attempt to compare the clinical characteristics of coronary thrombosis with those of myocardial infarction shows that coronary throm-

bosis and occlusion, per se, do not necessarily produce any characteristic clinical manifestations. If the occlusion occurs gradually, over months or years, with the concomitant development of an anastomotic circulation, no symptoms or signs will be produced and no myocardial lesions will be demonstrable. The syndrome usually called "coronary occlusion," which consists of prolonged substernal oppression or pain, a fall in blood pressure, pallor, cold perspiration, and other manifestations of shock, and is accompanied by electrocardiographic changes, fever, leucocytosis, and an increased sedimentation rate, in reality signifies myocardial infarction, and should be so termed.

Although myocardial infarction may occur with or without simultaneous, or immediately preceding, coronary thrombosis or occlusion, the clinical diagnosis of *myocardial infarction caused by acute coronary thrombosis* would appear to be justified if the sudden, severe, crushing pain and collapse occur under circumstances in which the work of the heart is not increased, i.e., during sleep or at rest, or under conditions, such as walking, which impose no greater burden on the heart than the patient has regularly borne satisfactorily in the past.

Attacks of severe, prolonged pain, associated at times with collapse, evidently result from prolonged insufficiency of the blood supply to the myocardium, and consequent anoxia. This "coronary failure" may occur with or without simultaneous, or immediately preceding, coronary thrombosis. If such "coronary failure" is sufficiently prolonged, myocardial infarction results. This eventuality may be obviated in some instances, however, if the demands on the myocardium are quickly reduced by rest in bed, sedatives, or the control of rapid ventricular rates. Sufficient collateral blood flow may be available to satisfy the thus lowered cardiac requirements and permit recovery of the anoxemic fibers. The duration of pain in such cases of coronary failure may be longer than that commonly seen in angina pectoris, but the persistent electrocardiographic changes, fever, leucocytosis, and increased sedimentation rate, which are characteristic of myocardial infarction, are not found.

6. THE RELATION OF THE SITE OF THE OCCLUSION TO THE LOCATION OF THE INFARCT

The site of the occlusion or occlusions in the coronary arteries bears no necessarily constant and immediately obvious relationship to the location of an infarct which may be found in the heart. Of course, in some instances, rapid occlusion of a single, major, coronary artery in an otherwise normal heart will cause infarction of the region obviously supplied by this artery (Cases 21 and 26). More often, however, in hearts with an anastomotic circulation there is no such direct relationship; instead, they may show occlusion of the right coronary artery and infarction of an area in the left ventricle which is normally supplied by the left circumflex or by the left anterior descending

artery (Cases 5, 8, 11, and 12). Similarly, occlusion of the left circumflex or left anterior descending artery may cause infarction of an area normally supplied by the other artery. The mechanism of this paradoxical phenomenon, "infarction at a distance," may be explained as follows:

The left anterior descending artery, for example, may be the site of arteriosclerotic involvement, progressing through gradual narrowing to final occlusion. Under such conditions there is a gradual development of collateral channels. The muscle normally supplied by the portion of the artery distal to the occlusion may continue to be adequately nourished, as evidenced by the absence of angina pectoris and myocardial fibrosis or infarction. The blood conveyed to this area through these anastomotic vessels may enter the left anterior descending arterial system from the left circumflex or right coronary arteries, or from the occluded artery itself, proximal to the occlusion. Gradual narrowing and occlusion may next occur in the left circumflex artery, as well as perhaps in the proximal portion of the left anterior descending artery nearer its mouth. The left ventricle, under such circumstances, will receive the major portion of its blood supply from the still relatively uninvolved right coronary artery. Such a heart, injected by the method used in this study, would show a purple injection mass in some of the vessels situated in the left ventricle. If, now, the right coronary artery suddenly becomes thrombosed, infarction of an area in the left ventricle would occur.

It is noteworthy that in this series, as in most other series, no example of infarction confined to the right ventricle was found, in spite of a large number of instances of occlusion of the right coronary artery. This is evidently because of the fact that the right ventricle, being thin-walled, may, like the auricles, derive considerable nourishment from the blood contained within its cavity.

7. THE IMPORTANCE OF VARIATIONS IN THE ANATOMIC DISTRIBUTION OF THE CORONARY ARTERIES

The effects of narrowing and occlusion of a particular vessel necessarily vary according to the importance of the vessel involved. A study of the 125 hearts in this series illustrates the diversity of the normal coronary arterial patterns.[35] Almost every possible variation in the length and importance of the three main coronary arterial branches was observed. These variations could be classified into three general groups: one with a balanced coronary circulation, and the other two with left and right coronary artery preponderance, respectively. In the group with the balanced coronary artery circulation, the right coronary artery supplied the right ventricle and part of the interventricular septum, and the left circumflex and left anterior descending arteries supplied the left ventricle and the rest of the septum. In the hearts with left coronary artery preponderance,

the right ventricle was, to an important degree, supplied by the left circumflex and left anterior descending arteries. In the group showing right coronary preponderance, the right coronary artery supplied a significant portion of the septum and left ventricle. The group exhibiting right coronary artery preponderance comprised approximately 40 per cent of the hearts, the balanced circulation group, another 40 per cent, and the group with left coronary artery preponderance, 20 per cent.

In any individual heart it was found that not only the location of an occlusion in a particular vessel was important, but that the role of that particular vessel in the blood supply of that heart was of great significance. Thus, in the group with left coronary arterial preponderance, comprising only 20 per cent of the hearts, the incidence of arterial occlusions was unusually high, and the incidence of infarction was highest. These infarcts generally resulted in death. Since in such hearts the left coronary artery supplied a relatively large part of the heart, and since the architecture of the coronary tree was such that the development of collateral circulation from the right coronary artery was difficult, these findings are not altogether surprising. In contrast, all but one of the infarcts in the hearts with a balanced circulation were healed infarcts, and two-thirds of those with right coronary artery preponderance were likewise healed. It may, therefore, be concluded that the clinical consequences of occlusions of the coronary arteries are significantly influenced by the original pattern of the coronary arteries in any particular heart.

8. THE RELATION OF POSTOPERATIVE SHOCK TO CORONARY THROMBOSIS AND CARDIAC DEATH

In several patients of this series acute coronary thrombosis was precipitated by postoperative shock. In a heart in which the coronary circulation is already impaired because of occlusions and narrowing, the sudden fall in blood pressure evidently leads to further stagnation, anoxemia, and, occasionally, to the formation of thrombi. Two patients (Cases 11 and 24), who died from shock caused by uncontrollable gastric hemorrhage from a carcinoma, and from postoperative shock following an operation for rectal carcinoma, respectively, were found at autopsy to have fresh thrombi which had been deposited independently in different coronary arterial branches. One patient (Case 11), 69 years of age, had had angina pectoris for four and one-half years. The right coronary artery was the seat of an old, long-standing occlusion, and the left anterior descending artery was greatly narrowed. In Case 24, likewise, there were extreme narrowing of two areas in the left anterior descending artery and an old occlusion of a primary branch of the right coronary artery.

In Case 1, death was caused by cardiac failure occurring during postoperative shock following amputation of a leg. No fresh occlu-

sions were found; the myocardial ischemia led to paroxysmal ventricular tachycardia and death. This patient, 67 years of age, had had angina pectoris for ten years, and showed old, complete occlusions of all three major coronary arteries.

Coronary thrombosis may occur not only because of stasis secondary to postoperative shock, but also in the course of severe, progressive, congestive failure. In Case 26, in the presence of general anasarca, acute thrombosis occurred simultaneously in the left anterior descending artery and in one of its major branches, and caused sudden death.

The foregoing cases are the only ones encountered in the entire series in which several fresh thrombi developed independently and simultaneously in different coronary arterial branches. The importance of avoiding a fall in blood pressure from any cause in cases of coronary arteriosclerosis is emphasized by the above observations. It is, perhaps, significant in this relation that coronary thrombosis occurs so frequently during sleep, when, likewise, the blood pressure is lowered.

9. THE RELATION OF THE PATHOLOGIC FINDINGS TO THE CAUSE OF DEATH IN PATIENTS WITH CORONARY ARTERY DISEASE

The various mechanisms by which coronary arteriosclerosis causes death may be conveniently discussed in four categories.

1. *Sudden death with the syndrome of "myocardial infarction."*—Myocardial infarction may be suddenly precipitated in a heart with but little arteriosclerosis if a thrombus develops rapidly in a major coronary artery. If the rate of development of narrowing and occlusion exceeds that at which a collateral circulation can be elaborated, infarction results. In other hearts, in which one or two arteries have become gradually occluded, collateral circulation, emanating from relatively uninvolved vessels, may prevent myocardial ischemia, as demonstrated by the absence of angina pectoris and infarction. When, however, the vessel or vessels which serve as the source of the collateral circulation also become suddenly occluded, circulation through anastomotic vessels either ceases or becomes inadequate because of the decreased head of pressure. Death may then occur suddenly, preceded by collapse, because of infarction itself, or because of cardiac softening and rupture, or because of cardiac standstill or ventricular fibrillation.

2. *Sudden death without the syndrome of myocardial infarction.*—In some of the cases in which gradual narrowing and occlusion of two or even three arteries were counterbalanced by the concomitant development of a collateral circulation, sudden death occurred without fresh thrombosis and without clinical manifestations or pathologic evidence of myocardial infarction. In some of these patients with gradually progressing coronary arteriosclerosis, certain areas of the heart evidently became irritable and gave rise to paroxysmal ventricular tachycardia, ventricular fibrillation, and death. Sudden death

without the syndrome of myocardial infarction also occurs because of simple asystole, in the absence of arrhythmias. Only occasionally, however, can one obtain conclusive electrocardiographic evidence of this sequence of events. In certain of our cases numerous ventricular systoles from multiple ectopic foci were observed shortly before death, a phenomenon recognized as a precursor of ventricular tachycardia and fibrillation. Certain other similar cases, not included in this communication, have been observed by us and will be reported elsewhere. In some instances these arrhythmias are the result of myocardial infarction; in other cases they are evidently caused by increased irritability produced by myocardial ischemia, without tissue necrosis.

3. *The syndrome of myocardial infarction, followed by gradually increasing congestive failure.*—Within one minute following the occlusion of a coronary artery in the dog the myocardial area rendered ischemic ceases to contract, and, if the ischemic area is sufficiently large, the remaining normal portions of the heart may be insufficient, and congestive failure may ensue.[32, 9] It is understandable that, in man, occlusion of a coronary artery supplying a considerable area favors the development of congestive failure, particularly if the rest of the heart is the seat of patchy fibrosis. Such patients may die, weeks or months following myocardial infarction, because of congestive failure. In others, acute pulmonary edema may cause death soon after the onset of myocardial infarction.

4. *The mechanism of death in cases in which coronary arteriosclerosis is a contributory factor.*—In some patients with coronary arteriosclerosis and a collateral circulation which is adequate under ordinary circumstances, lowering of the blood pressure caused by hemorrhage or postoperative shock may lead to sudden coronary failure, with myocardial ischemia and death. In other instances, left ventricular weakness, precipitated by causes not always discernible, may lead to cardiac asthma and, sometimes, death.

In general, it may be concluded that death occurs whenever a sufficiently large area of the myocardium undergoes ischemia, with or without necrosis, or when asystole, ventricular fibrillation, or congestive failure is produced by the ischemia. Such changes in the myocardium arise whenever there is a discrepancy between the nutritional requirements of the heart muscle, on the one hand, and the factors of supply, on the other hand.

The evidence suggests the advisability of rest in bed for at least several weeks for those patients, previously symptom-free, who suddenly develop angina pectoris, mild or severe, and for those patients who, having had angina pectoris, experience a sudden aggravation of their symptoms. Those patients who experience prolonged cardiac pain, but, on repeated examination, do not have a fever, leucocytosis, an increased sedimentation rate, or significant electrocardiographic changes may not require rest in bed for as long as six weeks.

Among those factors which decrease the nutritional supply to the myocardium, the following should be noted:

1. Narrowing and occlusion of the coronary arteries.
2. Lowered blood pressure, such as is observed in shock from any cause; also, the low diastolic blood pressure in aortic insufficiency.[36, 37]
3. Anoxia of the anemic (anemia), stagnant (congestive failure), or anoxic types (pulmonary edema, etc.).

Among those conditions observed in this study which increase the work of the heart and consequently increase its nutritional requirements, the following may be noted: (1) effort, (2) infection, (3) arterial hypertension, (4) cardiac hypertrophy, (5) valvular stenosis and insufficiency, (6) anoxia caused by pulmonary disease or anemia, and (7) tachycardia.

Throughout this communication the extraordinary significance of the collateral circulation in bridging this discrepancy between supply and demand has been emphasized.

VI. SUMMARY AND CONCLUSIONS

1. A joint clinical and pathologic study of 125 consecutive autopsy cases was undertaken in order to gain further insight into the clinical problems associated with angina pectoris, coronary thrombosis, myocardial infarction, and congestive failure; the clinical manifestations of these conditions were related to the pathologic changes observed in the coronary arteries and in the heart muscle. Thirty cases in this series, representing all of the patients with clinical evidences of cardiac pain or congestive failure, or with anatomic evidence of coronary occlusions, were carefully studied, and the findings compared with those in the remaining cases of the series.

2. In normal hearts, intercoronary anastomoses larger than 40 micra in diameter are not found. Anastomotic communications measuring less than approximately 40 micra in diameter exist between the coronary arteries of normal hearts; their presence can be demonstrated by the injection of watery solutions. These fine communications are probably of little functional significance in obviating the untoward effects of sudden coronary narrowing or occlusion.

3. Obstruction to normal coronary arterial blood flow by arteriosclerotic narrowing or occlusion regularly results in the development of intercoronary anastomoses measuring 40 to 200 micra in diameter. These are clearly demonstrated by the injection of a lead-agar mass. Anastomotic circulation develops, then, only when and where it is needed.

4. The development of such anastomoses is not related to age, for they are not present in the hearts of even senile patients when little or no coronary arteriosclerosis is present.

5. Such anastomotic circulation may so well compensate for occlusion or marked narrowing of a major coronary artery that the blood supply to the heart remains adequate for the ordinary activities of life. When the narrowing or occlusion progresses so far that the coronary circulation is insufficient to meet the needs of the heart during periods of increased work, myocardial anoxemia results. The "coronary reserve" is clearly reduced. The frequency of angina pectoris in patients who show such pathologic changes is in accord with these considerations.

6. In ten of the twelve cases, out of the total of 125, in which uncomplicated angina pectoris was the primary condition, there were old, complete occlusions of at least two main coronary arteries. In three of these instances all three main arteries had been occluded; in the remaining seven, the one unoccluded coronary artery was markedly narrowed. In the two hearts in this group in which only one main coronary artery was completely occluded, the other two main arteries showed marked arteriosclerotic narrowing. Fresh ante-mortem thromboses were not included in these analyses. The pathologic changes in every case of angina pectoris were in accord with the concept that angina pectoris is caused by paroxysmal, relative, myocardial anoxia.

7. Recent or old coronary occlusions were found in the absence of angina pectoris in thirteen of the 125 cases. Only twelve main coronary arteries had been completely occluded before the final illness in these thirteen cases, which is in contrast to the fact that in the twelve cases of angina pectoris twenty-five main arteries were found to be occluded.

8. In five cases of angina pectoris complicated by antecedent or coincident congestive failure, or by valvular disease, there were, on the whole, relatively few occluded coronary arteries. In these instances angina pectoris and congestive failure were caused predominantly by the greatly increased load on the heart. Three of the five patients had advanced rheumatic valvular disease, and one had cor pulmonale. A collateral arterial circulation had developed in the hypertrophied hearts of these patients. The presence or absence of pathologic changes in the coronary arteries was thus not always the sole factor which determined the presence or absence of angina pectoris or of coronary artery anastomoses.

9. The pathologic basis for congestive failure in patients with coronary arterial disease or angina pectoris was studied. The results suggest that constantly undernourished areas in hearts which are the seat of coronary arteriosclerosis, when subjected to still greater anoxemia, such as is brought about by exertion or emotion, undergo focal necrosis and a diffuse fibrous change. The replacement by connective tissue leads to myocardial weakness and congestive failure. The hearts with the greatest amount of replacement of myocardial fibers

by fibrous tissue were found in patients who, after some months or years of angina pectoris, finally developed congestive failure.

10. A comparative study of the clinical characteristics of coronary thrombosis and those of myocardial infarction forces the conclusion that coronary thrombosis and occlusion, per se, do not necessarily produce any characteristic clinical manifestations. If an occlusion occurs gradually, over months or years, with the concomitant development of an anastomotic circulation, no symptoms or signs will be produced and no myocardial lesions will be demonstrable.

11. The syndrome usually called "coronary occlusion," which consists of prolonged substernal oppression or pain, a fall in blood pressure, pallor, and the other manifestations of shock, and is accompanied by electrocardiographic changes, fever, leucocytosis, and an increased sedimentation rate, in reality signifies myocardial infarction, and should be so termed.

12. Attacks of severe, prolonged pain, associated at times with collapse, evidently result from prolonged insufficiency of the blood supply to the myocardium, and consequent anoxia. This "coronary failure" may occur with or without simultaneous, or immediately preceding, coronary thrombosis.

13. If such "coronary failure" is sufficiently prolonged, myocardial infarction results. This may be obviated in some instances, however, if the demands on the myocardium are quickly reduced by rest in bed, sedatives, or the control of rapid ventricular rates. Sufficient collateral blood flow may be available to satisfy the thus lowered cardiac requirements and permit recovery of the anoxemic fibers. The duration of pain in such cases of coronary failure may be longer than that commonly seen in angina pectoris, but persistent electrocardiographic changes, fever, leucocytosis, and an increased sedimentation rate, which are characteristic of myocardial infarction, are not found.

14. Although myocardial infarction may occur with or without simultaneous, or immediately preceding, coronary thrombosis or occlusion, the clinical diagnosis of myocardial infarction caused by acute coronary thrombosis would appear justified when the symptoms and signs of infarction occur under certain circumstances which have been discussed.

15. The site of an infarct in the heart bears no necessarily constant and immediately obvious relationship to the location of an occlusion or occlusions in the coronary arteries. The mechanism is described whereby, for example, a fresh occlusion of the right coronary artery may produce an infarct in the left ventricle, i.e., "infarction at a distance."

16. The clinical consequences of occlusions of the coronary arteries are significantly influenced by the original pattern of the coronary arteries in any given heart.

17. In the hearts of several patients in which the coronary blood flow was already reduced and presumably slowed because of occlusions and narrowing, the sudden fall in blood pressure which accompanied postoperative shock evidently led to further stagnation, anoxemia, and the deposition of multiple coronary thrombi. The importance of avoiding a fall in blood pressure, whatever the cause, in cases of coronary arteriosclerosis is emphasized.

18. In general, it is concluded that death occurs whenever a sufficiently large area of the myocardium undergoes ischemia, with or without necrosis; or when, because of ischemia, asystole, ventricular fibrillation, or congestive failure occurs.

19. Anoxia, necrosis, infarction, and fibrosis of the myocardium, and their accompanying clinical manifestations, arise whenever there is a discrepancy between the nutritional requirements of the heart muscle, on the one hand, and the factors governing nutritional supply, on the other. The extraordinary significance of the collateral circulation in bridging the discrepancy between supply and demand is emphasized.

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THE ACTIVATION OF RENIN BY BLOOD

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RENIN, a pressor substance extractable from normal kidneys, is a protein (Tigerstedt and Bergmann,[1] 1898). During the course of experiments on its purification (Helmer and Page,[2] 1939) it was found that as the preparation became more active, as tested in cats and dogs, it produced progressively less constriction of the vessels of the isolated dog's tail perfused with Ringer-Locke solution. It was, therefore, reasonable to suppose that some substance contained in blood might be necessary to enable renin to exert its pressor action. This was found to be correct, for if small amounts of blood, plasma, or plasma colloids were added, along with the purified renin, to the Ringer-Locke solution perfusing the tail, powerful vasoconstriction occurred.

This phenomenon was reminiscent of the activation of enzymes or the functioning of cosubstances. Although there is much similarity, there is no proof that this is so, hence we use the term "activator" merely to designate the substance which, acting on, or in conjunction with, renin, allows renin to exert its pressor action.

It needs to be emphasized that crude renal extracts produce constriction in the dog's tail and rabbit's ear, but this appears to be caused by heat-stable, dialyzable substances not present in purified renin.

METHODS

Principle

The experiment depends upon constant perfusion of oxygenated Ringer-Locke-acacia solution through an amputated dog's tail. The perfusate is collected and the volume and rate of perfusion recorded. Substances to be tested for vasoconstrictor action are injected into the perfusion fluid as it enters the caudal artery. Comparisons are then made between the extent and duration of reduction of flow caused by "control" and experimental injections.

Preparation of Dog's Tail for Perfusion

Tails were amputated from unselected street dogs. In general, small, thin dogs were most suitable. Preparations obtained from younger dogs were more responsive than those made from older animals.

Under ether anesthesia, a sagittal incision, 3 or 4 cm. long, was made through the skin and subcutaneous tissue of the ventral surface of the tail over the second, third, and fourth articulations. The caudal artery was secured, and tissue cleared from the artery by blunt dissection. The skin was dissected free from the surrounding tissue to form a flap of sufficient size to cover the stump after amputa-

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tion of the tail. The artery was cut between two ligatures, and the tail amputated by cutting through the third joint space with a sharp knife. Soft tissues were cleanly cut to avoid crushing the blood vessels.

Apparatus for Perfusion of the Tail

The amputated tail (*Q*) was placed in a glass cylinder surrounded by a water jacket (*O*), which supported the tail at an angle of 45° (Fig. 1). The arterial cannula (*K*) was connected by a short rubber connector to an upright tube (*H*), 10 mm. in diameter and 90 cm. high, which was surrounded by a water jacket. The tube contained a column of perfusing fluid, 60 cm. high, which was fed by siphon (*F*) from a two-liter beaker (*C*). The fluid in the beaker was warmed by circulating water through a glass coil (*D*), and oxygenated through tubes (*E*) and (*G*). A constant level was maintained in the beaker and in the upright tube by an inverted flask (*A*) supported by a tripod (*B*) at the level of the fluid in the upright tube. This modified form of Marriot flask kept the perfusion pressure constant.

Since the vessels of the dog's tail were very sensitive to changes in temperature, it was important that the temperature of the perfusion fluid be maintained at 38° C.

Perfusion fluid normally flowed through the caudal artery and out from the cut ends of veins and small anastomotic arteries at the proximal end of the tail. The existence of arterial anastomoses was shown by means of dissection and roentgenograms taken after injection into the caudal artery of a colored paste containing barium. These injection studies also demonstrated that perfusion fluid reached the most distal part of the tail.

The perfusate was collected in a balanced spoon (capacity 1.3 c.c.) (*N*), which, when filled, tipped and emptied, completing the circuit (*L*) of the signal magnet.

Test solutions were injected through the rubber cap of the side-arm (*J*) at the base of the upright tube, directly into the perfusing fluid, without interruption of flow. Resultant reduction in flow and duration of reduction were calculated from the kymographic record. Thus, 0.5 c.c. of 1:5000 tyramine solution reduced the outflow 70 per cent for four minutes; 0.5 c.c. of 1:500,000 adrenine solution reduced the flow 80 per cent, but the effect lasted only two minutes.

Preparation of Perfusion Fluid

Perfusion of the tail with Ringer-Locke solution alone resulted in a rapid decline in rate of flow as the tail became grossly edematous. This was about 50 per cent in one hour of perfusion. The addition of 7.5 grams per liter of purified acacia (30 per cent solution without sodium chloride, Eli Lilly and Company) to the Ringer-Locke solution allowed perfusion to continue for three or four hours, with a final decrease in flow of less than 10 per cent. Edema appeared more slowly. In fifty experiments, five hours of perfusion caused an average gain in weight of 0.35 gm. per gram of tail.

The formula of the perfusion fluid employed was:

Sodium Chloride	9.0 gm.
Potassium Chloride	0.42 gm.
Calcium Chloride	0.24 gm.
Magnesium Chloride	0.006 gm.
Sodium Bicarbonate	0.5 gm.
Dextrose	1.0 gm.
Acacia	7.5 gm.
Distilled water to make 1000 c.c.	

Preparation of Materials to Be Tested

Renin was prepared from fresh hog's kidneys by the method described by Helmer and Page[2] (1939).

Whole arterial blood, plasma, and filtrate of laked erythrocytes were used for comparison of their relative vasoconstrictor properties when injected alone and when mixed with renin. Arterial blood was withdrawn into a syringe containing mineral oil and heparin. The plasma obtained after it had been centrifuged for five minutes at 2400 revolutions per minute was drawn off and filtered through filter paper (Whatman No. 1). The residual erythrocyte mass, after removal of the plasma, was washed with normal saline, laked by adding two parts of distilled water to one part of cells (by weight), and the solution filtered. Each specimen of whole blood, plasma, and erythrocyte filtrate was tested at the beginning of each experiment, because these substances caused constriction if injected after several injections of renin had been made.

No specimen was used which, when injected in quantities up to 2 c.c., caused more than a 10 per cent decrease in perfusion. Careful and gentle handling of the arterial blood is essential in order to avoid the formation of vasoconstrictor substances in the blood.

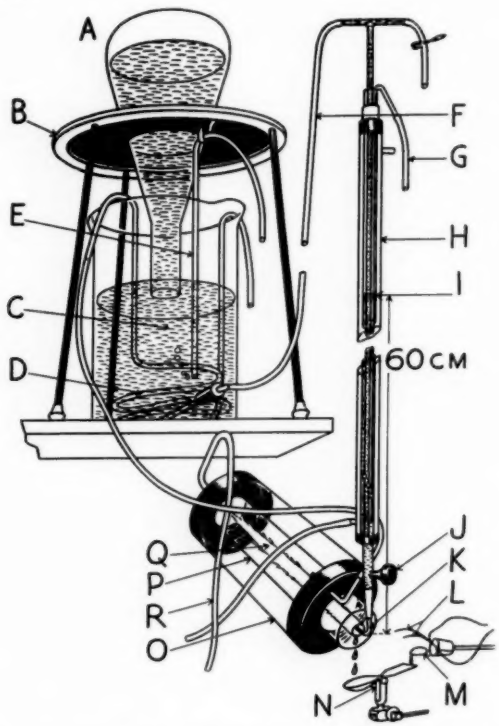

Fig. 1.—Apparatus for perfusion of isolated dog's tail with Ringer-Locke-acacia solution.

RESULTS

Action of Renin on Perfused Tail

The injection of 0.8 c.c. of *undialyzed* renin reduced the perfusion rate 90 per cent for four minutes. Boiling destroys the pressor action of renin in intact animals, but 0.8 c.c. of boiled renin reduced the perfusion rate 88 per cent for three minutes in the isolated tails. This suggested that the vasoconstriction observed in the isolated tail was not

caused by the protein pressor-principle, renin, but was due to the presence of other substances in the crude extract. The renin was therefore dialyzed for twenty hours against distilled water, and although it retained its full pressor action in intact animals, the injection of 2 c.c. of *dialyzed* renin did not alter the perfusion rate in the isolated preparation.

Action of Dialyzed Renal Extract (Renin) in the Presence of Blood

The injection of 20 c.c. of whole, heparinized, arterial blood did not reduce the perfusion rate, but the simultaneous injection of 1 c.c. of whole blood and 1 c.c. of renin reduced the perfusion rate an average of 80 per cent for three minutes in eight experiments. Since this reduction in flow might have been due to mechanical obstruction of blood vessels by packing of cells in whole blood, the experiments were repeated with plasma. Although 2 c.c. of plasma had little or no action, the injection of 0.5 c.c. of the same plasma, to which 0.5 c.c. of renin had been added, reduced the flow 83 per cent, and the vasoconstriction persisted for four minutes.

A similar effect was observed after the addition of renin to 0.5 c.c. of filtrate of laked erythrocytes. The perfusion rate was reduced by an average of 50 per cent for one minute in five experiments.

The injection of 8 mg. of cocaine made the blood vessels of the tail nonresponsive to tyramine (0.5 c.c. of a 1:5,000 solution), but did not inhibit the action of renin and plasma mixtures.

CONCLUSIONS

These experiments demonstrate that dialyzed renin is ineffective as a vasoconstrictor in the isolated dog's tail unless mixed with whole blood, plasma, or filtrate or erythrocyte protein. They therefore suggest that either whole blood, plasma, or filtrate of laked erythrocytes activates the vasoconstrictor action of renin, or that a latent vasoconstrictor substance in blood is activated by renin.

DISTRIBUTION AND PROPERTIES OF THE ACTIVATOR

The activating substance was present in both plasma and blood cells. Its presence was demonstrated in human, ox, rabbit, and cat's blood, as well as dog's blood.

It was thermolabile. Filtrate of boiled plasma did not activate renin. The activator gradually disappeared from blood which remained at room temperature for 5 or 6 hours. It was present in blood which had been stored for a week at 10° C. It did not pass through a 3 per cent, collodion, ultrafilter membrane.

The activator did not disappear from blood after bilateral nephrectomy. Seven days after bilateral nephrectomy, when the blood urea nitrogen was 256 mg. per cent, the plasma of a dog continued to activate renin. In another dog, plasma tested before and after bilateral nephrectomy showed an increase in its ability to activate renin.

The activating power of plasma was tested before and after hypophysectomy and no change was observed. The plasmas of two dogs which had been hypophysectomized in 1936 were tested in February, 1939, and at this time these plasmas were found to activate renin.

COMPARISON OF ACTIVATING POWER OF PLASMA FROM DOGS WITH NORMAL AND WITH ELEVATED ARTERIAL PRESSURE

The activating power of plasma was measured in 100 experiments by the relative vasoconstriction which occurred after the injection of 1 c.c. of renin and 1 c.c. of plasma obtained from dogs with normal arterial pressure and from fourteen dogs with experimental hypertension of renal origin (Table I). In eight of these animals hypertension was produced by clamping the renal artery (Goldblatt, Lynch, Hanzal, and Summerville,[3] 1934), and, in the remaining six, by wrapping the kidneys in cellophane (Page,[4, 5] 1939).

The range of variation in the activating power of plasma from normal dogs was greater than that of plasma from dogs with experimental hypertension (Table I, Columns A and B). Since experimental variations would affect to the same degree the action of plasma from normal dogs and plasma from dogs with hypertension, differences between the amount and duration of vasoconstriction were more significant than the actual amount of vasoconstriction produced by a single plasma and renin mixture (Table I, Column C). However, the average vasoconstriction and its duration were greater in all of the dogs with arterial hypertension than in the dogs with normal arterial pressure. These results suggested that plasma from dogs with increased arterial pressure has a higher content of activator than plasma from dogs with normal arterial pressure.

The activating power of plasma from dogs with hypertension increased to the same degree regardless of whether hypertension was produced by clamping the renal artery or wrapping the kidney in cellophane.

Changes in the activating power of plasma were followed in Dog No. 418 (Table II) during a normal control period, after uninephrectomy, and after application of a clamp to the renal artery. In four experiments performed in the control period (Jan. 4 to 23, 1939), preceding nephrectomy, the activating power of the plasma was slightly less than that of other normal dogs which were used as controls, and distinctly less than that of dogs with hypertension. Ten days after uninephrectomy the content of activator had not changed. Seven days after application of the clamp it had increased until it exceeded that of normal plasma, but was still less than that of plasma from dogs with hypertension. It continued to increase until, on Feb. 28, 1939, the activating power greatly exceeded that of normal plasma and equalled that of plasma from dogs with hypertension.

TABLE I

VASOCONSTRICTION PRODUCED IN AN ISOLATED DOG'S TAIL, PERFUSED WITH RINGER-LOCKE-ACACIA SOLUTION, BY INJECTION OF EQUAL QUANTITIES OF RENIN AND PLASMA OF DOGS WITH NORMAL AND ELEVATED ARTERIAL PRESSURE

(A) DOGS WITH HYPERTENSION						(B) NORMAL DOGS		(C) DIFFERENCE BETWEEN NORMAL AND HYPERTENSIVE DOGS	
DOG NUMBER	NUMBER OF EXPERIMENTS	AVERAGE MEAN INTRA-ARTERIAL PRESSURE MM. HG	DURATION HYPERTENSION PRIOR TO EXPERIMENTS MONTHS	AVERAGE REDUCTION FLOW PER CENT	DURATION CONSTRICTION MINUTES	AVERAGE REDUCTION FLOW PER CENT	DURATION CONSTRICTION MINUTES	REDUCTION FLOW PER CENT	DURATION CONSTRICTION MINUTES
Hypertension Produced by Clamping Renal Artery									
43	13	214	48	54.2	3.4	31.2	2.0	+23.0	+1.4
167	2	178	20	43.0	2.0	21.0	1.5	+22.0	+0.5
188	10	208	18	55.9	3.7	41.0	2.1	+14.8	+1.6
193	10	184	16	55.3	3.0	41.4	2.0	+13.9	+0.8
196	6	176	16	67.8	3.3	50.8	2.0	+17.0	+1.3
225	2	200	8	51.0	5.0	30.0	3.5	+21.0	+1.5
280	16	176	65	62.6	4.9	40.3	3.3	+22.3	+1.6
418	8	180	1	56.7	2.6	23.6	1.1	+33.1	+1.5
Hypertension Produced by Wrapping Kidney in Cellophane									
339	4	191	2	54.0	3.0	38.0	2.5	+16.0	+0.5
340	3	184	3	63.5	3.1	31.0	2.0	+33.7	+1.1
355	6	178	3	74.0	6.0	58.0	4.0	+16.0	+2.0
383	9	186	1	47.7	2.4	31.7	1.7	+16.0	0.7
379	5	198	1	52.5	2.7	17.5	1.2	+35.0	1.5
410	7	201	1	54.2	4.0	20.8	1.1	+33.4	+1.3

TABLE II

VASOCONSTRICTION PRODUCED BY RENIN AND PLASMA OF A DOG BEFORE AND AFTER ONSET OF EXPERIMENTAL HYPERTENSION, COMPARED WITH NORMAL DOGS AND DOGS WITH EXPERIMENTAL HYPERTENSION

DATE	DOG 418			NORMAL DOGS			DOGS WITH HYPERTENSION		
	AVERAGE MEAN INTRA-ARTERIAL PRESSURE MM. HG	REDUCTION FLOW PER CENT	DURATION OF CONSTRICTION MINUTES	AVERAGE MEAN INTRA-ARTERIAL PRESSURE MM. HG	REDUCTION FLOW PER CENT	DURATION OF CONSTRICTION MINUTES	AVERAGE MEAN INTRA-ARTERIAL PRESSURE MM. HG	REDUCTION FLOW PER CENT	DURATION OF CONSTRICTION MINUTES
1/ 4/39	112	23	1	140	26	1	186	59	2
1/ 5/39	100	15	1	128	25	2	210	54	3
1/ 6/39	112	33	2	140	40	2	160	62	3
1/19/39	128	23	2	125	27	2	170	37	4
1/23/39	Left nephrectomy								
2/ 3/39	146	29	2	110	34	2	186	42	3
2/ 8/39	Right renal artery clamped								
2/16/39	154	39	4	136	28	3	192	59	4
2/20/39	178	40	3	122	20	1	198	50	3
2/23/39	174	38	4	138	12	3	182	57	4
2/27/39	156	33	3	134	27	1	170	52	3
2/28/39	182	86	4	130	20	1	170	68	4
3/ 2/39	204	29	3	100	5	1	200	32	3
3/ 7/39	178	66	1	98	10	1	208	37	2
3/ 9/39	164	75	2	110	50	2	182	87	4
3/10/39	180	50	1	130	40	1	182	51	1+

The increased ability of plasma to activate renin which was observed in dogs with arterial hypertension showed no strict relationship either to the height of the mean arterial pressure or the duration of the hypertension. This phenomenon is not transient because it was present in Dog No. 43 four years after the onset of hypertension. The shortest time after the onset of hypertension that an increase in activating power was observed was one week after application of the clamp.

SUMMARY

(1) A useful method for perfusing a dog's tail is described.

(2) Purified renin, which produces a marked rise in arterial pressure when injected into intact animals, has little or no constrictor action on the vessels of a dog's tail perfused with Ringer-Locke-acacia solution. The addition of small amounts of whole blood, plasma, laked erythrocytes, or plasma colloids to purified renin causes intense vasoconstriction in the perfused tail.

(3) Partially purified extracts of kidneys contain heat-stable and dialyzable substances that cause constriction of the blood vessels of the dog's tail.

(4) The injection of sufficient cocaine to make the blood vessels nonresponsive to tyramine does not inhibit the action of renin-plasma mixture.

(5) Plasma from dogs after bilateral nephrectomy and hypophysectomy activates renin.

(6) Experimental hypertension produced in dogs by clamping the renal arteries or applying cellophane to the renal parenchyma appears to increase the ability of plasma to activate renin. There is no strict parallelism between the mean arterial pressure of the hypertensive animals and activator content of the blood.

CONCLUSIONS

Purified renin does not cause vasoconstriction in the absence of a heat-labile activator which is present in whole blood, plasma, erythrocytes, and plasma colloids from normal, hypophysectomized, and nephrectomized dogs. The activator appears to be increased in amount in plasma from dogs with experimental hypertension.

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Department of Clinical Reports

SPONTANEOUS RUPTURE OF THE AORTA

Direct Rupture of the Aorta Simulating Dissecting Aneurysm

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EXCLUDING the rupture of a saccular aneurysm, and in the absence of external trauma, rupture of the aorta is often designated as spontaneous.[1] It is said to occur once in about every five hundred autopsies.[2] The case described merits consideration because it was one of "spontaneous" rupture unassociated with dissection of the aortic wall, yet afforded a useful comparison of its clinicopathologic features with those found in the typical case of dissecting aneurysm.

CASE REPORT

The patient, W. S., a man 52 years of age, a news vendor, was admitted to Horton Hospital Sept. 13, 1937.

Family History.—His father had been an alcoholic. There was nothing else of importance.

Past History.—It was stated that he had had rheumatic fever at the age of 16. There was no history of syphilis. He had probably indulged excessively in alcohol when he was a young man.

History of Present Illness.—The patient's eyesight began to fail in 1934, but it was not until he was admitted to Fulham Hospital, in March, 1935, following an epileptiform attack, that taboparesis was diagnosed (the serological reactions were positive). No abnormality was found in the heart; the brachial blood pressure was 150/90. In August, 1935, he received a full course of malarial therapy. During the subsequent two years epileptiform seizures occurred occasionally. He was readmitted to hospital Sept. 3, 1937, in a state of collapse; he had had a convulsion while in his bed, twelve hours previously. When the heart was examined a musical second sound was noted at the base (there was no previous record of abnormal heart sounds). The rhythm was normal. Aortitis was suspected. Subsequently he had several fits, was extremely restless, and was doubly incontinent and irrational. He was removed to Horton Hospital.

Condition on Admission.—The patient was obviously ill. The apex beat of the heart was approximately in the nipple line at the fifth left intercostal space; the area of cardiac dullness was not enlarged; auscultation revealed a presystolic apical bruit and a faint early systolic murmur. The heart sounds at the base were distant, but otherwise appeared normal. No friction rub was detected and no friction sound heard. Examination of the respiratory system and abdomen revealed no abnormalities. There was incontinence of urine and feces. Neurologic signs typical of taboparesis were present. The patient was very confused and aphasic.

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Laboratory Data.—The specific gravity of the urine was 1.020; the urine contained a trace of albumin and some leucocytes. On Sept. 20, 1937, the blood Wassermann reaction was very strongly positive (+30+), and the Meinicke-Kahn reaction was fully positive (++++). On Sept. 27, 1937, the cerebrospinal fluid contained more than the normal number of cells and protein in the amount of 35 mg. per cent; it gave a positive (+6+) Wassermann reaction and a Lange test of 5544321000.

Progress.—Three days after admission the patient developed a low-grade pyrexia of an intermittent character which continued until his death. He remained in a feeble, restless, and confused state, groaning from time to time as if in pain, but indicating his lower limbs as being the site of the discomfort. The presystolic murmur which was heard on admission disappeared. No other abnormality in the heart was detected at any time. His general condition deteriorated, and, about one month after admission, in the early morning of Oct. 15, after a good night's sleep, he awoke, took some fluid, and a few minutes afterwards suddenly collapsed, gave a few gasps, and died.

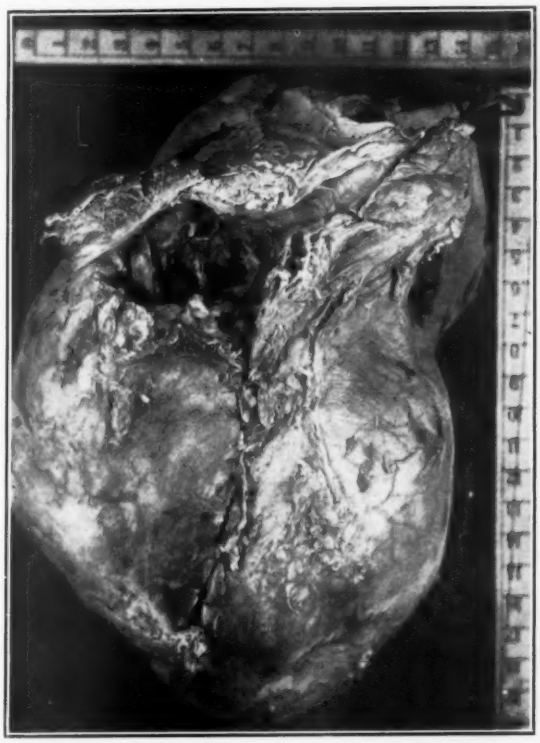

Fig. 1.—Reconstruction to show enormous distension of the pericardial sac. The external orifice of the aortic rupture is also visible.

Post-Mortem Findings.—The body showed considerable generalized wasting. The pericardium was found to be enormously distended (Fig. 1) and dark in color. The external measurements showed a maximum width of 15 cm. On incision, 800 gm. of dark, clotted blood were evacuated. The parietal layer of the pericardium was greatly thickened throughout; it was 0.5 cm. thick in the basal regions, and rather less in the apical portion. After washing out the cavity there still remained adherent to the heart a quantity of shaggy, partially organized clot, which was patchily distributed over its surface. Over the base of the heart this adherent clot

was more abundant, and its paler color indicated a more advanced stage of organization than elsewhere. The origin of the hemopericardium was also visible, and consisted of an opening in the anterior wall of the intrapericardial portion of the aorta (Fig. 2). This aperture was roughly diamond-shaped and had a breadth of 1½ cm. Its edges were hard and jagged.

The ascending portion and the commencement of the arch of the aorta showed a fusiform dilatation, extending from the aortic ring to the origin of the left subclavian artery. Its maximum internal circumference was 11.5 cm. The aortic ring itself was only slightly, if at all, dilated; the valve was competent and the cusps were healthy. The whole of the internal surface of the dilated portion of aorta was studded with yellowish, atheromatous plaques; these were slightly raised above the general intimal surface, but in only a few instances showed ulceration. In addition, slight longitudinal wrinkling of the intima was observed, and at about the junction of the ascending portion with the arch there was a small, pearly-white patch. The intra-aortic aspect of the opening into the

Fig. 2.—Shows the intrapericardial aspect of the aortic rupture, blood clot adherent to the surface of the heart, and much thickened pericardium.

pericardium, described above, was found to be situated 3.5 cm. above the anterior aortic cusp. It was rounded in shape, was 0.75 cm. in diameter, and had rough, calcareous margins. The opening was direct. There was no dissection of the aortic wall either at the point of rupture or elsewhere.

The descending thoracic and abdominal portions of the aorta showed less severe atheromatous changes, and there was no dilatation. The heart itself was of average size, and there were no changes indicative of valvular or coronary disease.

There was moderate atrophy of the anterior two-thirds of the cerebral hemispheres, but no evidence of any gross vascular lesion. There was some terminal, basal congestion of both lungs, and the liver was fatty and congested; there were no macroscopic changes in the other organs.

Microscopic Appearances.—Aorta: (a) Adjacent to the site of the rupture there were advanced atheromatous changes, but, in addition, there was definite evidence of syphilitic aortitis. In the media there was loss of elastic tissue; the laminae were irregular and to a large extent replaced by fibrous tissue. (b) The upper portion of the ascending aorta in the region of the pearly patch showed similar abnormalities, but the degenerative changes were much less pronounced. Pericardium: The thickening of the parietal pericardium consisted of fibrinous blood clot in its inner portion, newly formed fibrous tissue, with many fibroblasts, external to this, and an outermost layer of comparatively acellular fibrous tissue. These changes gradually merged one into the other, without any sharp line of demarcation. Brain: The Spatz iron reaction was positive, and there were moderate degenerative and inflammatory changes. Spinal Cord: Degeneration of the posterior columns characteristic of tabes dorsalis were present.

COMMENT

The discovery of an enormous hemopericardium at autopsy was unexpected in this case of taboparesis. The organization of the parietal pericardium and the organized clot at the base of the heart suggested that bleeding had occurred into the sac some time before the final, terminal hemorrhage. Certain considerations point to the possibility that the initial rupture of the aorta occurred during the epileptiform seizure on Sept. 3 (42 days before death). Thus, it was after this date that the patient's condition became grave. Signs of abnormality were discovered when the heart was examined—a new development, since the patient had been hospitalized frequently in the preceding two years. Moreover, none of the symptoms usually associated with rupture of the aorta were noted between the date of admission and of death. No dissection of the aortic wall occurred, and it is surmised that the initial rupture led to a partial hemopericardium. If this was so, a useful comparison can be made between our case and one of dissecting aneurysm.

The musical second sound at the base of the heart, and, later, the apical presystolic murmur, were interpreted as indicative of aortic regurgitation caused by syphilitic aortitis. At necropsy, one found a heart of average size and absence of actual aortic valvular disease or incompetence. Although Shennan[3a] states that physical signs of cardiac disease give little assistance in dissecting aneurysm and are noted in comparatively few cases, Hamman and Apperly[2] and Resnik and Keefer[4] state that characteristic signs of aortic insufficiency may occur in the absence of an organic valve lesion. Resnik and Keefer support the explanation advanced by Letulle,[5] namely, that the signs can be accounted for by the ebb and flow from the aorta into the aneurysmal pouch, but Hamman and Apperly do not accept this view; they think that there is probably a functional dilatation of the aortic ring. In our case the abnormal heart sounds could be explained by a

mechanism similar to that suggested by Letulle. In this instance the flow of blood might have occurred between the upper part of the pericardial cavity and the aorta.

Partial hemopericardium, not followed by death, has been described.[6, 7, 8, 9] Hardaway and Green,[6] in one of the few references to "direct" intrapericardial rupture of the aorta, cite a case in which they presume that the pericardial hemorrhage was first restricted by a line of old, visceroparietal adhesions. In their case the patient survived for six days, and, finally, "the primary rupture enlarged as a result of pressure, the retaining line of adhesions gave way, and the entire sac filled to extreme distension."

In our case one notes a past history of rheumatic fever.

In dissecting aneurysms the underlying process is said to be, in the majority of cases, a primary degeneration of the media.[3b] Shennan[3c] estimates that syphilitic mesaortitis was present in only 10 per cent of the series he analyzed. He points out that the fibrous replacement of the medial elements may actually tend to prevent free dissection. Klotz and Simpson (quoted by Narr and Wells[10]) hold a similar view. In our case the portion of aortic wall adjacent to the site of rupture showed advanced atheromatous changes, and the orifice of the rupture itself had roughened, calcareous edges, but the picture was complicated by an advanced syphilitic mesaortitis, producing a relatively dense, inelastic middle coat. Moreover, the position of the rupture within the intrapericardial portion of the aorta corresponded with the common situation of the primary tear in dissecting aneurysm. In the latter condition, a sudden rise of blood pressure as a result of severe physical strain is frequently the immediate exciting cause of the initial rupture, and, similarly, it would appear that this was so in the present case. One may speculate that the thin floor of an atheromatous ulcer yielded to the excessive force of the stream of blood, that ploughing-up of the media was prevented by the advanced fibrous changes, that the media itself gave way at the vulnerable spot, and that the size of the rupture at its intra-aortic aspect was smaller than at the "external" orifice and considerably smaller than the usual tear found in dissecting aneurysms. In the latter condition, Shennan[3d] states that a small tear favors longer survival; in our case, its small size and the nature of the pathologic changes in the media may in themselves have been underlying factors in the production of a partial hemopericardium.

We wish to thank Dr. W. D. Nicol, Medical Superintendent of Horton Hospital, for permission to report this case.

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PRIMARY, MASSIVE CALCIFICATION OF THE MYOCARDIUM

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PRIMARY, massive calcification of the myocardium is a relatively rare condition. Rupture through such a calcified region in the heart is sufficiently uncommon to justify reporting its occurrence.

With the exception of the intima of the coronary arteries, the endocardium and valves are the most frequent sites of calcium deposits in the heart. Involvement of the adjacent myocardium is a fairly common associated lesion, examples of which have been described fully by Martens,[1] Yater and Cornell,[2] and by Bishop and Roesler.[3] Of less frequent occurrence is the development of myocardial calcification through an inward extension of such a process in the pericardium. Early reports of such cases are those by Bordenave,[4] Lucas,[5] and Drummond.[6]

Two comprehensive reviews of the subject of myocardial calcification (Scholz,[7] Diamond[8]) have appeared during the past fifteen years. Most of the reports dealing with primary calcification of the heart muscle seem to be concerned with descriptions of minute calcium granules in degenerated muscle fibers. The majority of these deposits were said to be either toxic or inflammatory in origin. An unusual case was encountered by Niehaus,[9] in which a small calcium deposit in the myocardium, of unknown cause, produced occlusion of an otherwise normal coronary artery by external pressure, resulting in fatal infarction.

We have been able to find records of only fourteen instances of primary, massive calcification of the myocardium. Four of these were found among the six cases of myocardial ossification collected by Cohen and Levine.[10] The remainder are from reports by Askanazy,[11] Davidson,[12] Giepel,[13] Hirshboeck,[14] Moore,[15] Scholz,[7] Coats,[16] Diamond,[8] Hochrein,[17] and Determann.[18] Two of the cases collected by Cohen and Levine, one from Cutler and Sosman,[19] and the other from Simmons and Watson[20] are not included because of the evidence of pneumococcic pericarditis with an inward extension of the resulting pericardial calcification. So far as can be learned from the often meager data, coronary artery disease existed in all but four of these fourteen cases. No information regarding the state of the arteries was given by Topham[21] or Renauldin[22] (two of the cases referred to by Cohen and Levine), although Topham stated that the mouths of these vessels appeared healthy. In Coats' case there was calcification in areas of focal necrosis caused by pyemia and multiple abscesses complicating

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relapsing fever. Diamond reported the case of a 26-week-old premature infant with extensive calcium deposits in degenerate muscle. This he attributed to unknown toxic causes.

Our report concerns a patient with primary, massive calcification of the heart muscle which was evidently secondary to coronary disease. He presented the added, unique feature of spontaneous perforation through the center of this calcified infarct.

CASE REPORT

C. R., a 70-year-old white man, was admitted to the Cottage Hospital Oct. 9, 1938. He complained of hematuria of two years' duration, and of nocturia for several years. He gave no history of dyspnea, orthopnea, edema of the ankles, precordial pain, or of any gastrointestinal symptoms.

Physical Examination.—The temperature was 98.2° F., the pulse rate 85, the respiratory rate 20, and the blood pressure 115/85. The lungs were normal. The heart was slightly enlarged to the left. Auscultation of the heart showed that the aortic second sound was louder than the pulmonic second, and that there was a non-transmitted systolic murmur at the apex. The abdomen was slightly obese. There was tenderness over the left costovertebral angle. The reflexes were normal.

Laboratory Data.—The erythrocyte count was normal. The urine on admission and repeatedly thereafter contained pus, blood, and a moderate amount of albumin; there were no casts at any time.

Cystoscopic Examination.—The day after admission, cystoscopic examination showed that there was a large papilloma, with a sessile stalk, on the left side of the bladder just above the ureteral orifice. (This tumor could fold downward in such a way as to occlude the left ureteral orifice periodically). Slight enlargement of the prostate, with median bar formation, was noted. A bleeding vein on the surface of the bar was cauterized. A biopsy of the papilloma was made. Pyelographic studies, made by the retrograde method, showed no evidence of structural changes in either kidney. The left kidney pelvis appeared slightly larger than the right. Histologically, the bladder tumor was found to be a papilloma, but the possibility that it was malignant could not be ruled out.

Progress.—On Oct. 14 the patient complained of sharp pain in his left side. There was tenderness over the left costovertebral angle. The next day he became drowsy, but could answer questions in a rational manner. The leucocyte count was 16,000, with 83 per cent neutrophiles, and the urea nitrogen content of the blood was 27.2 mg. per cent. His speech was thick, and he complained of numbness in the fingers of the left hand, but had no weakness. At this time the temperature was 101.8° F., the pulse rate 98, and the respiratory rate 25. During the next two weeks his mind cleared and his abdominal distress disappeared, but the numbness of his fingers persisted. His fever subsided and the leucocyte count returned to normal. He was discharged Nov. 18 with a provisional diagnosis of a minor cerebrovascular accident, and was instructed to return a month or two later for removal of the bladder tumor.

On Dec. 9, 1938, the patient returned to the hospital complaining of severe pain in his left flank. He was slightly stuporous. Examination showed distention of the abdomen, with a palpable mass in the left upper quadrant. The leucocyte count was 43,000, with 96 per cent neutrophiles. The blood urea nitrogen was 21.6 mg. per cent. On Dec. 11 a large perinephritic abscess, containing 750 c.c. of greenish-yellow pus, was drained. From this pus, *Staphylococcus albus*, *Streptococcus viridans*, and *B. coli* were cultured. The patient showed

symptomatic improvement following the drainage, but his stupor continued. The leucocyte count diminished to 15,000, and the temperature fell to 99° F., by Dec. 19. He was given 500 c.c. of whole blood intravenously on Dec. 16 and again on Dec. 19. The drainage from the operative site diminished progressively, and on Dec. 20 all of the sutures were removed except those holding the drain. On Dec. 22 his pulse became weak and irregular, his hands cold and clammy. His temperature was 98.2° F., his pulse rate 95, his respiratory rate 25, and his blood pressure 122/88. His condition remained approximately unchanged for the next two days. On Dec. 25 he cooperated with the nurse in changing his bed and responded verbally to questions. He made no complaints. One hour later she found him dead.

Autopsy Report.—The body was that of a 70-year-old white man, five feet eight inches tall, weighing about 180 pounds. In each submaxillary region there was a soft, fluctuant mass which, on puncture, exuded thick, yellow pus. In the left flank there was a partially healed incision, 6 cm. long, which drained a scant amount of purulent fluid. The right pleural cavity contained 500 c.c. of a thin, cloudy fluid resembling a transudate, and the left, 400 c.c. of a similar fluid.

The pericardium contained 500 c.c. of partially clotted blood; the epicardial surface was opaque and slightly granular. In some places it was covered by adherent fragments of clotted blood, in others by fine, granular, fibrinous exudate. An aneurysmal sac, 5 cm. in diameter, projected from the apex of the left ventricle. It was attached to the parietal pericardium by fine, fibro-fibrinous adhesions, and showed a ragged rent in its wall. This sac was formed by the external fibers of the left ventricular myocardium and by the adjacent, thickened epicardium. The wall was 1 mm. thick at the tip, and contained numerous thin plaques of calcium. Adherent to its inner surface were masses of fibrin, erythrocytes, and soft, gray debris. The lumen of the sac communicated with the chamber of the left ventricle through a circular orifice 1 cm. in diameter (Fig. 1). Surrounding this ventricular defect was a ring of calcified material, 1.5 cm. thick, resembling, on section, a trabeculated osseous structure. The papillary muscles adjoining this calcified ring were hyalinized at their points of contact with it. The endocardium was thin and transparent. Strands of dense fibrous tissue extended into the myocardium adjacent to the ring for only short distances. Elsewhere the myocardium showed only rare strands of fibrosis. The wall of the left ventricle was 2 cm. thick, and that of the right, 1 cm. The valves were delicate. The coronary arteries contained thick foci of patchy calcification (Fig. 2). Injection with a radiopaque material showed that the major branches of the left coronary artery were markedly narrowed, but still patent (Fig. 3). The entire aorta was atheromatous to an advanced degree, with ulceration and calcification. The arch exhibited minor degrees of intimal wrinkling. The heart weighed 650 Gm.

The left kidney weighed 180 gm. It lay in indurated perirenal fat. Dissecting sinuses and small cavities in the latter contained small amounts of thin pus and communicated with the operative incision. The capsule stripped with ease. The cortex and medulla were of good thickness, pale and mottled. The left ureteral wall was thickened, but its lumen admitted a 1 mm. probe throughout its entire length. The right kidney and ureter were not remarkable. From the bladder mucosa, just above the orifice of the left ureter, a soft, pedunculated polypoid mass, 3 cm. in diameter, hung. This mass had a narrow base. The lungs, gastrointestinal tract, liver, spleen, pancreas, prostate, adrenals, lymph nodes, and skeleton were essentially negative.

Microscopic Examination.—Hematoxylin-eosin stain was used routinely. Heart: A section taken from the left posterior ventricular wall, well above the calcified ring, showed inflammatory thickening of the epicardium. This was characterized by a fibroblastic proliferation and an infiltration of the edematous epicardium with lymphocytes and plasma cells. Fibrin which contained agglutinated erythrocytes

was adherent to the roughened epicardial surface. Hemosiderin granules were encountered only occasionally beneath the surface. Numerous neutrophiles were mixed with the fibrin, but showed no tendency to form foci. A similar pericardial reaction was present on the auricles. Gram stains showed cocci in clusters and pairs scattered in the fibrin on the surface. The myocardial fibers of the ventricle were thickened. In sections removed from the vicinity of the calcified ring, the myocardial fibers exhibited various phases of transformation into amorphous hyaline strands. Sections through the calcified ring revealed dense, amorphous bundles of collagen. At random in this tissue, sheet-like, pale, and dark blue areas with serrated edges, resembling calcium, were encountered. Osteoid tissue could not be

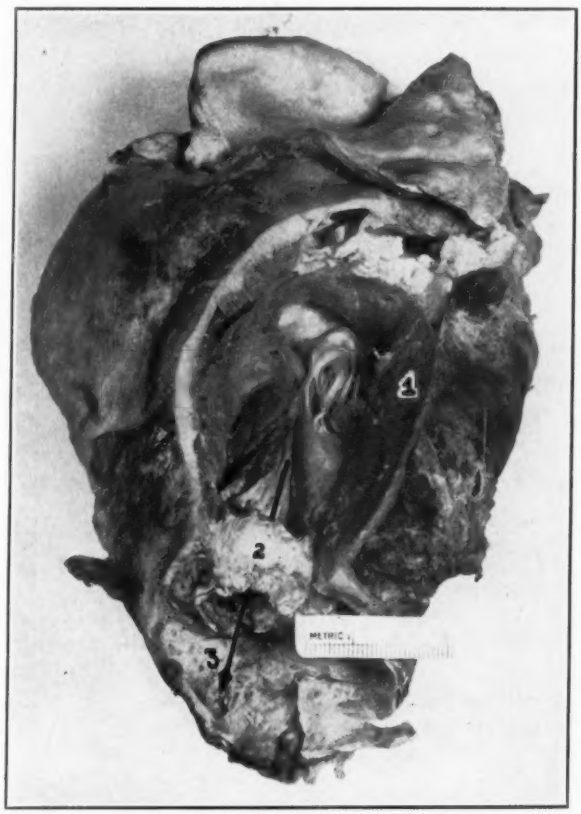

Fig. 1.—Heart after removing a portion of the anterior wall of the left ventricle. *1*, Left ventricular myocardium; *2*, Calcified ring through which the left ventricle ruptured. An arrow is placed through the open center of the ring; *3*, Partially calcified inner wall of the aneurysm.

demonstrated in association with the calcium deposition. In the areas near the ring, several small arteries of the epicardium were either partially or totally occluded by marked medial hypertrophy. Section through the aneurysmal sac below the ring showed that the aneurysmal wall was composed of dense, partially calcified, hyaline tissue. The ragged inner surface of the aneurysm was covered with masses of disintegrating fibrin and leucocytes. Wedged into crevices of the aneurysmal wall were focal collections of leucocytes and bacteria, similar to those seen on the epicardium. Section through the main branches of the left coronary artery showed marked intimal hyalinization and calcification. The major branches of the left

were narrowed to about one-third of the normal. In the right kidney, beneath the capsule, a few scars, with lymphocytes and hyalinized glomeruli, were noted. The tubules occasionally contained hyaline casts. Sections of the left kidney exhibited numerous collections of lymphocytes and plasma cells in the intertubular stroma. Leucocytes could be seen next to some of the tubules, which usually contained necrotic cellular debris. The picture was one of chronic pyelonephritis. The left ureter showed hypertrophy of its musculature. The papilloma of the bladder was

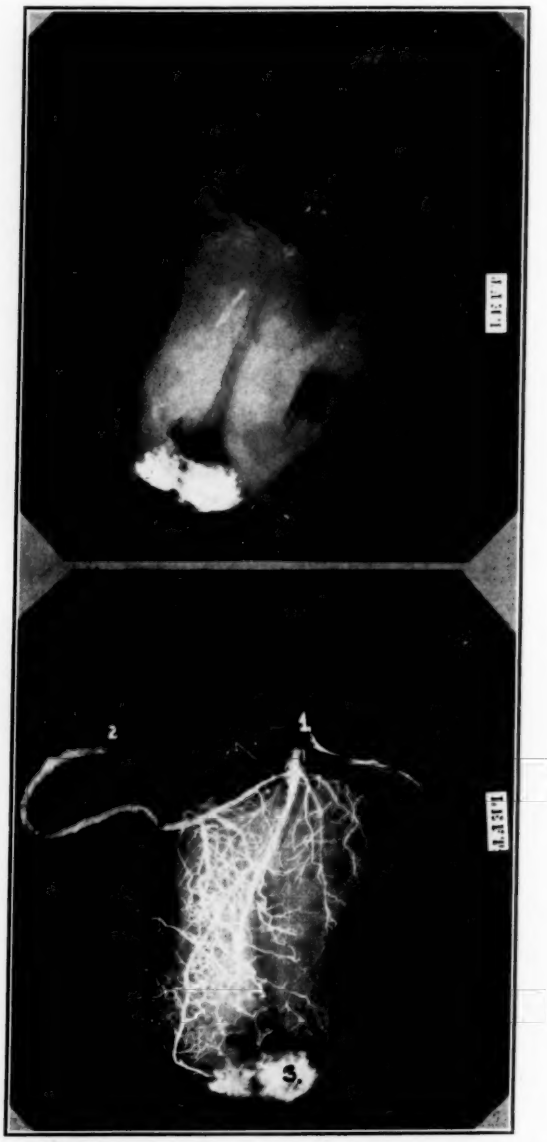

Fig. 2.—Anteroposterior roentgenogram of the necropsy specimen. Note the large calcium deposit at the apex and the calcium shadows in the walls of both coronary arteries.

Fig. 3.—The specimen after injecting the coronary arteries with a barium mixture. *1*, Point of injection of the two branches of the left coronary artery; *2*, Point of injection of the right coronary artery; *3*, Calcified myocardial infarct.

composed of delicate connective tissue cores, lined with a few layers of stratified, transitional epithelium. No mitoses were noted, and invasion of the submucosa could not be demonstrated, confirming the diagnosis of papilloma.

INTERPRETATION

It seems clear that the large, calcified area in the apex of the left ventricle represented a healed or healing infarct, as indicated by its location as well as the coexistent, occlusive, coronary sclerosis.

The fact that complete central calcification of the apical infarct did not occur probably predisposed to the gradual erosion and subsequent development of the mural aneurysm. The presence of hyalinized sheets of tissue showing patchy calcification suggests that the growth of the calcification was slow. The development of the aneurysm and its subsequent rupture present greater difficulties of interpretation. A complicating element requiring consideration is the exudative and early proliferative reaction in the pericardium. The presence here of bacteria which were similar to those in the aneurysmal lining suggests that the origin of the inflammatory processes in the two locations was identical, and that they developed simultaneously. The most likely primary focus for a bacteremia was the perinephric abscess, which contained both streptococci and staphylococci. The submaxillary abscesses no doubt constituted other, secondary foci. It is possible that the bacterial infection led to rupture of the aneurysm. Bacterial invasion of the tissue in the center of the calcified ring may have so weakened it that the aneurysmal dilatation was a natural result.

DISCUSSION

This case presents three unusual features. Although massive myocardial calcification, painless coronary occlusion, and spontaneous cardiac rupture are not in themselves particularly rare, the combination of the three in the same case must be extremely unusual, if not unique.

Massive myocardial calcification usually follows occlusive coronary disease. There was definite evidence of coronary sclerosis in ten of the twelve cases collected from the literature in which any information was given regarding the condition of the coronary arteries. Figs. 2 and 3 demonstrate sclerosis and partial occlusion of both coronary arteries and comparative avascularity of that portion of the heart wall supplied by the left coronary artery.

The absence of angina with such an extensive lesion is interesting. Kennedy[23] reported that in 200 autopsy cases of cardiac infarction he found a definite history of pain in only 91 per cent of the recent, and 63.7 per cent of the old, infarcts. In twenty-seven, or 13.5 per cent, of the 200 cases there was no history of pain or distress of any kind.

Although spontaneous cardiac rupture is considered rare by some observers, it is not an unusual cause of death in cases of recent coronary

infarction. In the last 400 consecutive autopsies done by one of us the condition was encountered four times. Evans[24] found, among 10,000 autopsies at the Los Angeles County General Hospital, twenty-seven spontaneous ruptures, all of which had occurred in patients suffering from fresh myocardial infarcts. Rupture of the heart following healing of an infarct is much less likely to occur. Even when myocardial aneurysms have formed, their rupture, according to Parkinson, et al.,[25] is an uncommon event. We have been unable to find any instance of rupture of a calcified myocardial infarct similar to the one reported here.

SUMMARY

1. A case of cardiac rupture through a calcified myocardial infarct, with the intermediate formation of a myocardial aneurysm, is reported. It is suggested that bacteremia resulting from a perinephric abscess, with localization of the inflammatory process in the myocardial aneurysm, brought about this unusual event.

2. Coronary sclerosis is the most common cause of primary, massive, myocardial calcification; its etiologic relationship has been established in ten of fourteen cases reported in the literature and in our own.

The authors wish to thank Dr. W. D. Sansum for permission to report this case, and Drs. M. J. Geyman and R. Gates for the roentgenologic work.

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Department of Reviews and Abstracts

Selected Abstracts

Boone, Bert R.: An Amplifier for Recording Heart Sounds Through the Use of the Cathode-Ray Tube. J. Lab. and Clin. Med. **25**: 188, 1939.

A description is given of a heart sound amplifier which uses a cathode-ray tube as a recording device for reproducing in the form of photographic tracings the sound patterns emanating from the functioning heart.

AUTHOR.

Rodbard, S., and Katz, L. N.: The Elimination of the Effect of the Chemical Mediator of Renal Hypertension. Am. J. M. Sc. **198**: 602, 1939.

Removal of the ischemic kidney in hypertensive dogs with a normal kidney remaining in situ results in a return to normotensive levels within six hours. The time period for this return might have been prolonged because of interference by the fleeting neurogenic hypertension which often follows nephrectomy.

Removal of the ischemic kidney in hypertensive dogs with no kidney remaining results in a considerably slower return to the normal pressure levels, averaging in our series five times that found when a normal kidney was left in situ.

These results suggest that the chemical mediator of hypertension due to renal ischemia is destroyed, neutralized, or otherwise eliminated at a rapid rate only in the presence of normal kidney tissue.

Our results indicate that normotension is independent of renal action, while renal hypertension depends upon the kidney for its genesis, continuation, and elimination.

AUTHORS.

Sanders, Alexander: Experimental Localized Auricular Necrosis. An Electrocardiographic Study. Am. J. M. Sc. **198**: 690, 1939.

The effect of localized auricular necrosis upon the electrocardiogram of the dog was studied, to help elucidate the changes in the auricular complex and minor changes in the ventricular complex occurring in coronary disease.

Necrosis near the sinus node resulted in a nodal rhythm, wandering pacemaker, auricular extrasystoles, and paroxysmal auricular tachycardia. Localized left auricular necrosis frequently produced elevation of the auricular S-T segment in Lead I with an upward bowing and an auricular Q wave. In two instances, intra-auricular block resulted. In a few instances of left auricular necrosis, similar auricular S-T changes occurred in the esophageal lead, to the exclusion of Lead I. Right auricular necrosis produced similar auricular S-T changes in the esophageal lead and in Leads II and III. Changes in the initial auricular complex (P wave proper) consisted of broadening, inversion, diminution or increase in amplitude, and slurring, notching, the development of a Q or S wave, or M or W shapes.

Some cases of localized auricular necrosis failed to alter the electrocardiogram, while others produced minor changes in the ventricular complexes. The similarity of such induced areas of localized auricular necrosis to clinically occurring auricular infarction was considered, and the possible clinical import of the results discussed.

AUTHORS.

Holt, J. P., and Lawson, Hampden: The Relationship Between Vascular Volume and Blood Flow in the Hind Limb of the Dog. Am. J. Physiol. **127:** 492, 1939.

It is generally agreed that in organs whose volume is free to change, vasoconstriction with reduction in the flow of blood is accompanied by a reduction in the volume of the organ; and conversely, that vasodilatation with an increase in the flow is accompanied by an increase in the volume of the organ.

It was believed that enclosure of the hind limb of a dog in rigid container would produce conditions comparable to those of the cerebral circulation which is naturally in a more or less rigid enclosure, the cranium, and that in this way certain problems concerning regulation of cerebral circulation might be studied. Fixation of the limb was accomplished by application of a tight plaster of Paris cast to the shaven hind limb of the dog or the limb was tightly bandaged and fixed with negative pressure in a plethysmograph. The object was to discover whether enclosing the limb by these methods, either of which would keep the volume of the limb constant, would reduce the vasomotor response of the limb to constrictor and dilator drugs.

Blood flow through the hind limb of eleven dogs anesthetized with ether or sodium barbital was measured by the direct venous outflow method, a differential manometer method, and a modification of the method of Wagner and Livingstone. Intra-arterial injections of epinephrine decreased and intra-arterial injections of nitroglycerine increased the flow. The change in flow with these drugs was approximately the same when the limb was free to change its volume as it was when the volume was fixed.

STEELE.

Hoff, Hebbel E., Smith, Paul K., and Winkler, Alexander W.: The Relation of Blood Pressure and Concentration in Serum of Potassium, Calcium, and Magnesium. Am. J. Physiol. **127:** 722, 1939.

The relation between changes in blood pressure and concentration of potassium, calcium, and magnesium salts, injected slowly and continuously until death, was studied in twenty-four dogs and eleven cats. In addition electrocardiographic changes and skin temperatures were noted.

Potassium and calcium salts produced only minor changes in the blood pressure until terminal cardiac failure occurred, while injections of magnesium produced an immediate fall in blood pressure, due presumably to a marked vasodilator action shown by an immediate rise in skin temperature. Potassium and calcium did not exhibit any such effect. The vasodilator effect of magnesium was due in part to a change of the concentration of circulating magnesium and in part to the actual presence of an elevated concentration.

STEELE.

Thomson, William A. R.: The Effect of Potassium on the Heart in Man. Brit. Heart J. **1:** 269, 1939.

Potassium salts, in the form of the chloride and the citrate in doses varying from 3 to 30 gm. daily, have been given to twenty-four patients with various disease, and the effect on the electrocardiogram has been observed.

In fourteen of these the administration of potassium salts was followed by an increase in the height of the T wave in one or more leads. No correlation was found between the increase in the height of the T wave on the one hand and the amount of potassium given or the increase in the concentration of the serum potassium on the other hand, except that in the fourteen patients who showed this change the average increase in the level of the serum potassium was 8.3 mg. per 100 c.c., compared with 2.6 mg. per 100 c.c. in the patients who showed no such change.

In one patient the T wave, which was diphasic in all leads before the administration of potassium salts, became more deeply diphasic while they were being given.

In two patients definite degrees of heart block were produced by the administration of potassium salts. In one, there was prolongation of the P-R interval, while in the other sinoauricular block and nodal rhythm resulted with marked slowing and irregularity of the heart rate.

The similarity of these changes to those produced by vagal stimulation, by acetylcholine, and by pitressin is discussed, and the hypothesis is advanced that in each case they may be mediated through the action of the potassium ion on the myocardium.

Certain clinical applications of this work are also discussed, and it is recommended that potassium salts should be used with the utmost caution in patients with cardiovascular or renal disease.

AUTHOR.

Dill, D. B., Johnson, R. E., and Daly, Cornelius: Metabolic and Cardiovascular Effects of Intramuscular Injections of Adrenalin and Amphetamine. Am. J. M. Sc. **198:** 702, 1939.

Intramuscular injections of adrenalin in normal fasting men either did not change or slightly increased the proportion of carbohydrate utilized during the period in which blood sugar and lactate were elevated. Acetone bodies in blood and urine fluctuated within the normal range. Amphetamine did not modify carbohydrate utilization or the concentrations of sugar, lactate, or acetone bodies in the blood. It had a calorigenic effect that was smaller in magnitude but more sustained than that of adrenalin. The rise in systolic blood pressure after amphetamine was greater in one subject, and in all subjects was more sustained than after adrenalin. In contrast with adrenalin, amphetamine produced a small but consistent rise in diastolic pressure.

AUTHORS.

Reynolds, Samuel R. M., and Foster, Francis I.: Peripheral Vascular Action of Estrogen in the Human Male. J. Clin. Investigation **18:** 649, 1939.

The effect of intramuscular injection of estrogen upon the volume and skin temperature of the finger was measured in a group of twenty adult human male subjects.

Approximately two-thirds of the subjects showed an effect involving an increase in finger-volume, commencing a few minutes after injection and continuing from thirty to sixty minutes. A plateau level was attained which is sustained for the period of observation (maximum time up to two hours). The average percentage increase in finger-volume was 4.6. No change in skin temperature was noted in such cases.

Injection of the corn oil vehicle alone (as an unknown) had no such effect on finger-volume in these subjects.

The character of the response, along with other established facts regarding the vascular effects of estrogen, indicates that it depends upon dilatation of the small vessels in the skin beyond the arterioles. There is no measurable increase in the rate of blood flow in the skin.

The failure of estrogen to bring about dilatation of the skin vessels in some subjects is unexplained.

AUTHORS.

Stead, Eugene A., Jr., Kunkel, Paul, and Weiss, Soma: Effect of Pitressin in Circulatory Collapse Induced by Sodium Nitrite. J. Clin. Investigation 18: 673, 1939.

Pitressin in man was ineffective in experimental collapse induced by sodium nitrite and tilting because it did not cause an increase in venous tone, and because the arteriolar constriction produced by the drug tended further to reduce tissue blood flow.

The intramuscular injection of 1 c.c. of pitressin with subsequent tilting of the subject to the upright position produced collapse ending in syncope in two of the six normal subjects tested.

In two subjects in whom collapse was induced in the upright position by the administration of sodium nitrite, pitressin did not prevent the development of collapse and in one of these it hastened it. In one subject, in whom neither sodium nitrite nor pitressin in the upright position produced collapse, sodium nitrite followed by pitressin induced profound collapse ending in syncope. In still another subject neither sodium nitrite nor pitressin, singly or combined, produced syncope.

Pitressin, given in doses of 0.5 or 1 c.c. to normal subjects in the horizontal position, produced abdominal cramps, ashen pallor, and a marked decrease in blood flow both in the hand at 32° and that at 43° C. It produced no change in venous tone in the hand, heart rate, or arterial pressure.

Pitressin slowed the blood flow in the hand to such a degree that water at a temperature of from 43° to 45° C. felt distinctly uncomfortable, and in one case caused the skin to be blistered at 45° C.

Sodium nitrite produced circulatory collapse and syncope in the upright position in about 50 per cent of a large group of subjects tested. No criteria have been developed to predict the postural response of any given person to the administration of sodium nitrite.

AUTHORS.

Kunkel, Paul, Stead, Eugene A., Jr., and Weiss, Soma. Effect of Paredrinol (a-N-Dimethyl-p-Hydroxyphenethylamine) on Sodium Nitrite Collapse and on Clinical Shock. J. Clin. Investigation 18: 679, 1939.

From theoretical consideration paredrinol (a-N-dimethyl-p-hydroxyphenethylamine) should be effective in preventing the sodium nitrite collapse induced in the upright position because paredrinol increases the venous tone without at the same time increasing the metabolism of the tissues or causing marked arteriolar constriction.

In four normal subjects the intramuscular injection of 25 mg. of paredrinol prevented the collapse induced in the upright position by sodium nitrite. In three others it had no effect.

In two subjects with severe postural hypotension, symptoms of cerebral anoxia were prevented by the use of paredrinol.

In seven of the ten cases in severe clinical shock resulting from infectious disease, the intramuscular or intravenous injection of from 15 to 50 mg. of paredrinol caused a rise in arterial pressure. Only two of these cases showed definite clinical improvement.

In one patient paredrinol was effective both in the collapse induced by an acute streptococcal pharyngitis and in the collapse subsequently induced by motionless standing.

The responses of the patients in severe clinical collapse differed from those in the normal subject as follows: (a) From two to four times the amount of paredrinol was required to cause a significant elevation of blood pressure, and even then the arterial pressure rarely increased to hypertensive levels; (b) the heart rate was usually increased instead of decreased; (c) repeated doses of the drug, when given

after the blood pressure had returned to normal, failed to be as effective as the original injection.

Paredrinol is a useful drug in the treatment of collapse caused by the pooling of blood within a dilated venous system. This study suggests, however, that in shock resulting primarily from loss of fluid from the blood stream the drug may not be helpful, or it may even be harmful.

AUTHORS.

Eichna, L. W., and Bordley, James: III. Capillary Blood Pressure in Man. Comparison of Direct and Indirect Methods of Measurement. J. Clin. Investigation **18**: 695, 1939.

Two methods of measuring capillary blood pressure in man were compared: (a) the indirect pressure-capsule method of Danzer and Hooker, and (b) the direct microinjection method of Landis. The comparison was made both at normal and at elevated levels of venous pressure.

When a cuff encircling the upper arm was inflated to pressures below diastolic arterial pressure, the venous pressure in the hand rose. The extent of the rise was influenced by the difference in level between the cuff and the hand.

The capillary blood pressure in the nail fold, recorded by the direct method, was found always to exceed the venous pressure in the hand.

The capillary blood pressure in the nail fold, recorded by the indirect method, failed to show any correlation with the venous pressure in the hand.

It has been concluded that of the two methods only the direct one affords an accurate measurement of capillary blood pressure.

AUTHORS.

Mortensen, Vagn: Pathogenesis of Bundle Branch Block. Nord. med. tidskr. **2**: 1971, 1939.

A brief review of the newer literature concerning bundle branch block has been made.

The electrocardiograms in standard and precordial leads in sixteen cases of bundle branch block have been described. It has been pointed out that there exists a great deal of conformity between the ventricular complexes in Lead IVF in complete left bundle branch block (new terminology) and in Lead CF_2 in complete right bundle branch block and in curves belonging to Bayley's groups; this may suggest that curves belonging to Bayley's groups are representing complete right bundle branch block.

Attention has especially been drawn to the diminution or the absence of the R wave in Lead CF_2 in left bundle branch block. A similar configuration has been found in pronounced left ventricular preponderance. On account of this observation the hypothesis has been advanced that the normal relation between the amplitudes of the R waves in CF_2 and IVF depends on a certain normal relation between the conduction through the two ventricles, and that the diminution of the R wave which may be found in pronounced left ventricular preponderance and especially in left bundle branch block is caused by a lesser or greater relative delay of the conduction system or owing to a hypertrophy of the left ventricle.

In standard leads the changes characteristic for pronounced left ventricular preponderance have formerly been explained partially by the hypertrophy of the left ventricle, partially by changes in the heart's position caused by the hypertrophy and finally—owing to the resemblance between these curves and bundle branch block—by intraventricular conduction delay, which with the old terminology for bundle block must be localized to the right ventricle. These causes—the hypertrophy

of the left ventricle and intraventricular conduction delay—could with the old terminology for bundle branch block only with difficulty be looked at from the same point of view.

The new terminology for bundle branch block is bringing quite new perspectives for the understanding of the preponderance curves. The plain transition which consists between left preponderance curves and left bundle branch block (new terminology) makes it most likely that pronounced left preponderance curves are caused by a lesser degree of delay of the conduction through the left ventricle than is the case in left bundle branch block. Such a lesser degree of delay of the conduction is in most cases explainable by the hypertrophy of the left ventricle. The new terminology for bundle branch block is so bringing the different theories about the cause to preponderance curves into a more likely connection with each other than is allowed by the old terminology. Surely hypertrophy of the left ventricle is a very essential factor in most cases of pronounced left preponderance curves and the delay of conduction is then secondary hereto, but drawing forward the relative delay of conduction as the immediate cause to the preponderance curves it will be possible to explain also the cases of preponderance curves which are not accompanied by hypertrophy of the left ventricle as a delay of conduction must not necessarily be due to a hypertrophy but may be due to lesions in the conduction system.

Attention has been drawn to the fundamental difference between absence of the R wave in CF_2 in left bundle branch block or pronounced left ventricular preponderance curves and absence of the R wave in anterior wall infarction. In left bundle branch block we have to do with a diminution of the R wave, eventually a complete absence of this wave, whereas in anterior wall infarction we have to do with appearance of a new initial negative deflection (a Q wave) at the same time as the R wave is reduced in amplitude, eventually quite disappears. According to this a remnant of the R wave in CF_2 in left bundle branch block will present itself as a small initial positive deflection, while in anterior wall infarction it will present itself as a splitting in an initial negative deflection.

Attention is drawn to the fact that the special form of "left preponderance" curve (often with negative T_3) caused only by a horizontal position of the heart may not be treated by the reflections which have been done in this paper.

AUTHOR.

Mortensen, Vagn: Analysis of the QRS Complex in Precordial Leads in Cases of Anterior Wall Infarction. Nord. Med. Tidskr. 3: 2749, 1939.

Precordial leads CF_2 and IV F were employed in twenty-three cases of infarction of the anterior wall of the heart; 192 curves were taken. The QRS complex showed an initial positive deflection in both of these leads in only one instance. The first QRS deflection was negative in both leads in twenty of the twenty-three cases. In two cases there was an initial negative deflection either in CF_2 or in IV R in all records. The presence of an initial negative deflection (Q) is therefore a very constant finding in anterior infarction.

Only in classical ("central curves") is the presence of an initial negative deflection associated with complete absence of the R wave. There are QRS complexes of other types ("marginal curves") equally characteristic of infarction which begin with a negative deflection but in which R is not absent. It is therefore misleading to speak of the disappearance of R as the chief abnormality of the QRS complex of precordial leads produced by anterior infarction. In these leads anterior infarction produces two changes in QRS: (1) the appearance of a Q wave, and (2) a complete or partial disappearance of the R wave. The first of these changes is strikingly constant, the second extremely variable. When the disappear-

ance of R is partial, notched, split, or W-shaped complexes result. The difference between these curves and those in which R is absent is a difference only in degree.

There are two ways in which a classical (''central'') infarction curve may develop from the normal diphasic QRS complex: (A) In the first the R wave is reduced in size and eventually disappears; (B) in the second, a new initial negative deflection (Q) develops simultaneously with the diminution and eventual disappearance of R. In a previous paper it has been pointed out that a transformation of QRS of the first kind occurs in some instances of pronounced left ventricular preponderance and also in left bundle branch block, and the hypothesis was advanced that under these circumstances the diminution and disappearance of R is due to delay in conduction through the left ventricle. The resulting QRS complexes may be referred to as ''false infarction curves.'' The curves which result from the transformation of QRS described under (B) may be called ''true infarction curves.'' A remnant of R in left ventricular preponderance or left bundle branch block presents itself as a small initial upward deflection; in anterior infarction a remnant of R presents itself as a notch in an initial negative deflection.

As a practical matter it is important to regard the QRS changes in precordial leads produced by infarction as distinguished by the presence of an initial negative deflection. While this change may be associated with a reduction in R, or its disappearance, the latter is not distinctive. An abnormally small initial R wave may be found in anterior infarction, but it represents a considerable deviation from the typical changes in QRS produced by this condition.

Spillane, John D., and White, Paul D.: Herpes Zoster and Angina Pectoris. Brit. Heart J. **1:** 291, 1939.

Twelve instances of the occurrence of herpes zoster in anginal subjects are described. In ten of these the zoster appeared after the anginal attacks had become established. In two the zoster first appeared about two years before the first anginal paroxysm. In both these, as in the former group, a close association was apparent between the distribution of the herpetic eruption and that of the anginal pain.

Attention has been drawn to the occurrence of herpes zoster over the area of referred pain from other diseased viscera also, viz., the pleura, pericardium, gall bladder, kidneys, stomach, and appendix. It is suggested that repeated bombardment of spinal root ganglia by afferent impulses from the ischemic heart gives rise to antidromic impulses that lead to vasodilatation and blister formation in referred cutaneous areas. The herpetic eruption is thus a trophic manifestation of disease of the coronary vessels in these cases.

AUTHORS.

Burch, George E., and Voorhies, Norton W.: A Study of the Incidence of Coronary Occlusion and Angina Pectoris in the White and Negro Races. Am. J. M. Sc. **198:** 685, 1939.

A study of the medical case histories at Charity Hospital of Louisiana from 1928 through 1937 revealed a relatively low incidence of coronary occlusion and angina pectoris in the negro as compared with the white race. Of 162 instances of coronary occlusion, 138 (85.2 per cent) were white (121 males and seventeen females), and twenty-four (14.8 per cent) were negro (twenty-two males and two females); of the thirty-two instances of angina pectoris, twenty-nine (90.7 per cent) were white (24 males and five females) and three (9.3 per cent) were negro (all males). After the data were corrected for the difference in admission, the ratios of white to negro for the incidence of coronary occlusion and angina pectoris were found to be 7 to 2 and 4 to 1 respectively. Some of the factors which might influence the incidences of the two diseases in the white and negro races are discussed.

AUTHORS.

Sheehan, H. L., and Sutherland, A. M.: Sex and Age Factors in Acute and Chronic Valvular Disease. Brit. Heart J. 1: 303, 1939.

A statistical analysis was made of the pathologic and clinical findings in 1057 necropsies on patients with acute or chronic valvular lesions, to ascertain the sex and age differences.

Chronic Rheumatic Valve Lesions.—There was a very high incidence of pure mitral lesions in young girls and of combined lesions affecting the tricuspid in women from 15 to 35. In males, combined aortic-mitral lesions were common throughout life, but tricuspid involvement was rare. The age of death in chronic mitral lesions was about the same as in chronic aortic-mitral lesions, but patients with chronic tricuspid lesions tended to die much earlier, nearly always as a result of congestive failure.

Recurrent Endocarditis.—Simple acute vegetations, developing on an old valve lesion, or, less often, spreading to previously undamaged valves, were very common in childhood but progressively less frequent with advancing age. The recurrent endocarditis was rather more frequent in females; it was very common in acute rheumatism or congestive failure, but was sometimes found with intercurrent diseases. The mitral and aortic were involved with about equal frequency, the tricuspid less commonly.

Simple Acute Endocarditis.—This was rare under 5 years of age. It was more common in older children, associated with acute rheumatism or chorea or sometimes with acute infections or septic conditions. In adults the endocarditis was usually associated with infections or miscellaneous conditions; in old age it was usually a terminal occurrence in carcinoma or cardiorenal disease. In acute rheumatism the lesion usually affected multiple valves: in nonrheumatic cases it usually affected the mitral alone, particularly in females, or the aortic alone, particularly in males; combined lesions were uncommon.

Ulcerative and Subacute Endocarditis.—This was rather commoner in males than in females. When occurring on previously normal valves it was usually of septicemic type in early life; but in old age it was often only terminal, usually in association with carcinoma of the stomach or uremia.

When developing on previously scarred valves it was commoner in middle life, particularly in males, and was usually of septicemic type; it was common on chronic aortic but rare on tricuspid lesions.

Primary Sclerosis and Syphilis.—This affected the aortic valve and was commoner in males than in females.

It is difficult to obtain any real correlation between the incidence of acute endocarditis, recurrent endocarditis, and the chronic valve lesions. Some of the acute lesions may lead to subsequent scarring of the valves, and some of the recurrent lesions to increase of the fibrosis in scarred valves or to the scarring of previously normal valves. The evidence on this matter is, however, inconclusive.

AUTHORS.

Futcher, Palmer Howard, and Scott, Virgil C.: Four Cases of Gonococcal Endocarditis Treated with Sulfanilamide, with Recovery of One. Bull. Johns Hopkins Hosp. 65: 377, 1939.

One patient suspected of having gonococcal endocarditis of the pulmonic valve recovered following treatment with transfusions and sulfanilamide. The criteria for establishing the presence of a bacterial endocarditis were not completely fulfilled. However, the cardiac findings in the presence of a positive blood culture and the nephritis made it seem likely that the patient suffered from a gonococcal endocarditis probably involving the pulmonic valve.

Three additional patients, all proven by positive blood culture and subsequent autopsy to have gonococcal endocarditis, died despite treatment with sulfanilamide.

AUTHORS.

Vander Veer, Joseph B., and Norris, Robert F.: The Electrocardiographic Changes in Acute Pericarditis. J. A. M. A. **113**: 1483, 1939.

The characteristic electrocardiographic pattern which is found in many cases of acute pericarditis is described and illustrated by three cases of acute pericarditis resulting from different etiological factors.

The electrocardiogram of acute pericarditis is not frequently confused with that of acute myocardial infarction. The two conditions, however, can be differentiated on the basis of the electrocardiogram alone, in practically all cases. The changes which are seen result from a subepicardial myocarditis and are often transient in nature, lasting only a few days. There is little or no relationship between the amount of pericardial effusion present and the electrocardiographic changes.

Precordial leads are of value in confirming the findings in the standard leads in acute pericarditis, but experience has shown that Lead IV R (apex and right arm) is more valuable than Lead IV F (apex and left leg) in demonstrating the acute electrocardiographic changes (R-T segment elevation) in this condition.

AUTHORS.

Brotchner, Robert J.: Etiology of Hypertension Resulting from Coarctation of the Aorta. Arch. Path. **28**: 676, 1939.

Coarctation of the aorta is described as observed in five adults. The condition was diagnosed in three of them during life.

An experiment is presented in which acute hypertension was produced by stenosis or occlusion of the aorta at a level above the origin of the celiac artery. The hypertension experimentally produced is shown to be independent of the kidneys.

The similarity of this acute experimental hypertension to that accompanying coarctation of the aorta in adults is discussed, and further clinical and experimental evidence is pointed out to show that the hypertension associated with coarctation of the aorta is also due to mechanical obstruction and not to renal ischemia with its "pressor substance."

AUTHOR.

Rennie, Thomas A. C.: The Role of Personality in Certain Hypertensive States. New England J. Med. **221**: 448, 1939.

A group of patients with hypertension are reported in whom emotional factors play a precipitating role or influence the course of the disease. Attention to the personality component proved of definite value in lowering the blood pressure in those patients in whom it was still modifiable. Psychotherapy in hypertension is a positive mode of attack, often the only really effective one available.

NAIDE.

Schroeder, Henry A., and Steele, J. Murray: Studies on "Essential" Hypertension. Arch. Int. Med. **64**: 927, 1939.

Two hundred and eighteen cases of so-called "essential" hypertension have been studied and classified from the standpoint of the varied phenomena which have been observed. Five main groups have been tentatively distinguished on the basis of the criteria used: (1) renal; (2) nervous; (3) endocrine; (4) vascular, and (5) unclassified. These groups exhibit disorders in the same systems as do those in which secondary arterial hypertension is found.

This study suggests that "essential" hypertension is not a primary disease. The fact that this diagnosis is made by exclusion should indicate evidence that many causes are possible. In too many instances the associated disturbances may be significant. The unity of "essential" hypertension is, therefore, seriously called into question. In the light of this recital the need for a new classification is obvious. The present classification cannot be regarded as more than tentative. It has already been of advantage in facilitating diagnosis, in making prognosis more accurate, and in setting the indications for therapy on a more reasonable basis. It is desirable that other means of differentiation be utilized to establish what is "essential" in this condition.

AUTHORS.

Engle, David E., and Binger, Melvin W.: The Response in Blood Pressure of Hypertensive Patients to Acetyl-Beta-Methylcholine. Am. J. M. Sc. **198**: 609, 1939.

These observations demonstrate that the peripheral blood vessels of most hypertensive patients react by a greater proportional dilatation in response to the administration of acetyl-beta-methylcholine than do the blood vessels of normal individuals. It is difficult to understand how peripheral blood vessels which display a hyperdilatation in response to the administration of choline derivatives can be maintained in a state of increased tone in the case of hypertensive individuals, unless it is assumed that the concentration of acetylcholine at the nerve endings of the cholinergic vasodilator nerves of these patients is subnormal. Observations support the hypothesis that a deficient acetylcholine-vasodilator mechanism may be a factor in the production of the arterial hypertension of men. It would seem that this approach to the study of mechanisms for the production of hypertension deserves further investigation.

AUTHORS.

Chesley, Leon C.: The Variability of Proteinuria in the Hypertensive Complications of Pregnancy. J. Clin. Investigation **18**: 617, 1939.

It is assumed that dividing the concentration of urinary protein by the ratio of urinary creatinine to plasma-endogenous creatinine will give the concentration of protein in the glomerular filtrate, or a value proportional to it.

Four urine specimens, collected at intervals of an hour, were taken from six pregnant and five nonpregnant nephritics, and from four eclamptic and nine preeclamptic patients. The "protein filtration" was calculated, and the variability from hour to hour was determined.

In nephritics, pregnant or not, the protein filtration shows very little variation from hour to hour. In toxemia of pregnancy, the protein filtration is variable. It is suggested that this argues for a functional cause (vascular spasms) for the proteinuria.

AUTHOR.

Parkinson, John, Bedford, D. Evan, and Almond, S.: The Kinked Carotid Artery that Simulates Aneurysm. Brit. Heart J. **1**: 345, 1939.

An aneurysm-like swelling on the right side of the neck, the so-called kinked carotid, is described on the basis of forty-seven cases and a review of the cases published previously.

The common form of kinked carotid is generally associated with hypertension —often with hypertension combined with arteriosclerosis—but sometimes with arteriosclerosis alone (25 per cent). It occurs in middle-aged and older women, especially

in those affected by spinal curvature and obesity, and it is scarcely ever seen in men. The swelling itself produces no symptoms beyond local throbbing; it changes little if at all in the course of years, and it has no bearing on prognosis. X-ray examination shows elevation of the aortic arch due to lengthening and uncoiling of the aorta, aided by a high diaphragm. Attention is drawn to an abnormal shadow sometimes cast by the kinked carotid, which partly obscures the apex of the right lung.

A comparable vascular swelling may be associated with aortic incompetence, coarctation of the aorta, and other congenital vascular anomalies.

The swelling consists of an arterial prominence with tortuosity in the region of the innominate bifurcation, which is often elevated. It may be formed by a loop of the right carotid, though the innominate itself or even the subclavian may contribute. Atheroma of the aorta and these branches is usually present, but not syphilis. The dynamic factor, accentuated by hypertension, is important in the production of the swelling. The necropsy findings in three cases are reported.

Differential diagnosis is discussed chiefly in reference to aneurysm of the right common carotid artery, for which it is frequently mistaken. The occurrence of isolated aneurysm of the proximal portion of the carotid artery, unless traumatic, is doubted; surgical operations performed for such an aneurysm most often discover no more than a kinked carotid.

AUTHORS.

Garvin, Curtis F., and Siegel, Mortimer L.: Cor Pulmonale Due to Obstruction of the Pulmonary Artery by Syphilitic Aortic Aneurysms. Am. J. M. Sc. **198:** 679, 1939.

Heart failure due to syphilitic aortic aneurysms is usually caused by dilatation of the aortic valve ring with resultant aortic insufficiency. Heart failure due to obstruction of the pulmonary artery from pressure of a syphilitic aortic aneurysm is an extraordinary occurrence. Three such cases and similar ones previously reported permit the following conclusions:

The aortic aneurysm may be large or small. It bulges anteriorly and to the left, thereby compressing the pulmonary artery.

The pulmonary artery is obstructed by either simple pressure, a viselike action, or by erosion of the aneurysm into the lumen (without rupture).

The heart shows hypertrophy and dilatation of the right side thus constituting in terms of modern terminology a cor pulmonale.

Clinically, myocardial insufficiency, especially of the right side of the heart is evident. The aneurysm may or may not give physical signs of its presence. Roentgen studies show the aneurysm in such a position that it could press on the pulmonary artery and the electrocardiograms reported show right axis deviation. Under such circumstances and if all other causes of heart failure are excluded, the diagnosis can be considered probable.

AUTHORS.

Thomson, K. Jefferson, Reid, Duncan E., and Cohen, Mandel E.: Studies on Circulation in Pregnancy. IV. Venous Pressure Observations in Normal Pregnant Women, in Pregnant Women with Compensated and Decompensated Heart Disease, and in the Pregnancy "Toxemias." Am. J. M. Sc. **198:** 665, 1939.

The arm venous pressure, as measured by the method of Moritz and von Tabora, is within "normal limits" during normal pregnancy. This study corroborates the studies of others who find the venous pressure in normal pregnancy within normal limits and points out possible sources of error in those studies which report increase

of venous pressure in normal pregnancy. The venous pressure of normal pregnant women tends to diminish from early pregnancy to the sixth month, remains fairly constant throughout the remainder of pregnancy, rises slightly in the early puerperium and returns to the early pregnancy level later post partum.

This same trend is present in pregnant women with compensated heart disease. The measurement of venous pressure cannot be used to predict or diagnose early congestive heart failure in pregnant cardiac women.

There is probably a slight increase in venous pressure accompanying "toxemia" of pregnancy. The venous pressure decreases immediately post partum in patients with "toxemia" of pregnancy, in contrast to normal pregnant women in whom it usually rises. This study does not corroborate the finding of extremely high venous pressures in "toxemias" of pregnancy.

AUTHORS.

Perry, Thomas M., and Langsam, S. M.: Incidence of Fatal Cardiovascular Disease in Charleston, S. C. Arch. Int. Med. **64:** 971, 1939.

In a series of 2,066 consecutive autopsies performed in Charleston, S. C., all cases in which death was from cardiovascular disease have been studied, using the clinical record, the autopsy protocol and, in many instances, the microscopic slides. These cases were then classified according to etiologic factors. Hypertensive cardiovascular disease was the etiologic factor in more than half the cases. When only cases of congestive heart failure were studied, it was noted that hypertensive cardiovascular disease again more than equaled all other etiologic types of heart disease combined. The incidence of hypertension was particularly high in the Negro race, and especially in the Negro male. While hypertension was common in the white race also, arteriosclerotic disease (without hypertension) was almost as frequently a cause of death. Syphilitic cardiovascular disease was seldom encountered in the white patients in this series.

Each etiologic group of cases of vascular disease was further divided according to the manner of death, and the average age at death was shown. In almost every category the Negro died earlier of vascular disease than did the white patient.

Coronary thrombosis, either with or without hypertension, was seldom encountered in the Negro, but in the white group it was common.

An attempt to classify the cases of hypertensive cardiovascular disease according to the factors bringing about hypertension met with little success.

The annual variations in deaths from hypertensive cardiovascular disease in this locality were studied, and the oscillations in the graph were shown to be greater than would be expected if chance alone were the important factor. This offers a lead for consideration in attempts to learn the cause of hypertensive disease.

Seasonal variations in deaths from hypertensive diseases also were shown, but these variations could be accounted for by chance error.

AUTHORS.

Corrigendum

The name of the author of "The Significance of Myocardial Scars in the Human Heart," *J. Path. and Bact.* **49:** 195, 1939, of which an abstract was published in the December, 1939, issue of the JOURNAL, Vol. 18, page 766, is not T. C. Lowell, but T. E. Lowe.

Book Reviews

FAILURE OF THE CIRCULATION: By Tinsley Randolph Harrison, M.D., Associate Professor of Medicine, Vanderbilt University School of Medicine. Ed. 2, 502 pages, 61 figures, $4.50, Baltimore, 1939, The Williams and Wilkins Company.

The second edition of this book, which appears four years after the first, has been enlarged by one hundred six pages. "Forward failure" and "backward failure" have replaced the less familiar terms "hypokinetic syndrome" and "dyskinetic syndrome." Discussions of cardiac syncope and cardiac collapse have been added. The section on "angina pectoris" has been considerably expanded.

A book inevitably reflects the viewpoint of its author. Dr. Harrison, for a number of years, has been an active investigator of the physiology of the circulation in the laboratory, and a keen observer of patients at the bedside. Both of these aspects of his work are apparent in each chapter. Throughout there is correlation between disturbances in function and the clinical manifestations of disease. Reference is made to theoretical considerations, but the author is careful to distinguish between facts which are based upon evidence, and hypotheses which, though reasonable, for the present lack confirmation.

By forward failure is meant that type of circulatory disturbance in which the symptoms result from an insufficiency of the blood supply to the tissues. Three types are distinguished, characterized respectively by collapse, syncope, or sudden death. In the group of patients who are likely to die suddenly are included those who suffer from anginal pain.

Backward failure is used synonymously with congestive heart failure. The section dealing with this topic occupies over half of the book.

The mixed type of circulatory failure is briefly mentioned; in this condition, in which there is sudden and widespread damage to the heart, as in coronary thrombosis, forward and backward failure occur simultaneously.

In the chapter on general circulatory disturbances without failure, the overactive heart and cardiac neurosis are described. The volume concludes with a summary, in which circulatory disorders are considered as disturbances in hemodynamics. There is a large bibliography which has been brought up to date.

The book contains an enormous amount of information, much of which is based upon Dr. Harrison's own observations. The style is clear and the presentation logical. The monograph is heartily recommended to all who are interested in the study of the circulation. It can be read with profit, and, it is fair to add, with pleasure, both by investigator and practitioner.

ROBERT L. LEVY.

APARATO CIRCULATORIO: By Pedro Cossio, M.D., Profesor Adjunto de Semiología de la Facultad de Medicina de Buenos Aires. El Ateneo, Buenos Aires, 1939, second edition, 407 pages, profusely illustrated.

The second edition of "Aparato Circulatorio" will be read with much interest in the United States, even by those who already know the edition of 1935.

This book was written with the purpose of putting together all that is known about physical examination and special techniques for the study of the heart and vessels.

In a short chapter are briefly described the structure of the heart, the properties of the myocardium, the laws of the heart and vessels, and the pathology of heart disease.

One chapter is devoted to history taking, one to general examination, and one to examination of the heart. Then comes a detailed description of electrocardiography, followed by chapters on roentgenologic examination of the heart, and on methods for measuring arterial pressure, venous pressure, and circulation time.

The ninth and tenth chapters describe graphic records of the arterial pulse and the venous pulse, and functional tests. The last chapter describes in detail the disorders of the cardiac mechanism.

The book is well assembled and shows more than 300 interesting pictures and records.

One of the most valuable chapters is that which deals with auscultation and phonocardiography. The description and the records draw largely from the best South American contributions, among which some of the author's (i.e., Cossio) are well known.

The chapter on roentgenologic study of the heart is perhaps too short, considering the importance of the method, but is completed by many clear sketches and photographs.

There is lack of a description of methods for registering graphically the blood pressure in man, as well as absence of any mention of mechanical and electrical exploration of the heart by way of the esophagus (some of the best studies on this subject were published in the Argentine), and too short a description of blood pressure changes and methods for studying the circulation time. These few shortcomings do not detract from the value of the book, for it is very difficult to present all that is known on heart and blood vessel examination without writing a book on the diseases of these structures as such.

ALDO LUISADA.

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THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

**Executive Committee.*